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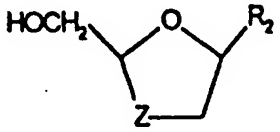
(54) Title: PROCESS FOR PREPARING SUBSTITUTED 1,3-OXATHIOLANES WITH ANTIVIRAL PROPERTIES

(57) Abstract

Disclosed are processes for preparing compounds of formula (I) and pharmaceutically acceptable salts or esters thereof, wherein R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and Z is S, S=O or SO_2. The invention also relates to intermediates of use in the preparation of these compounds.



(I)

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PROCESSES FOR PREPARING SUBSTITUTED 1,3-OXATHIOLANES WITH ANTIVIRAL PROPERTIES

This application is a continuation-in-part of application serial no. 07/564,160 filed August 7, 1990, which is a continuation-in-part of applications nos. 07/308,101 filed February 8, 1989, and 07/546,676 filed June 29, 1990.

The present invention relates to processes for preparing substituted 1,3-oxathiolanes with antiviral activity and intermediates of use in their preparation.

BACKGROUND OF THE INVENTION

Nucleosides, and in particular, 1,3-oxathiolanes and their analogues and derivatives are an important class of therapeutic agents. For example, a number of nucleosides have shown antiviral activity against retroviruses such as human immunodeficiency viruses (HIV), hepatitis B virus (HBV) and human T-lymphotropic virus (HTLV).

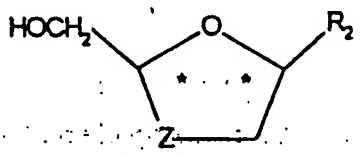
The most potent anti-HIV compounds thus far reported are 2',3'-dideoxynucleosides, more particularly, 2',3'-dideoxy cytidine (DDC) and 3'-azido-2',3'-dideoxythymidine (AZT). These compounds are also active against other kinds of retroviruses such as the Moloney murine leukemia virus. However, clinically, both compounds are toxic.

A structurally distinct class of compounds known as 2-substituted-5-substituted-1,3-oxathiolanes has now been discovered and found to have superior antiviral and antiretroviral activity without cell toxicity. See, e.g., EP 0382526A and WO 91/17159.

Because of the increasing incidence and the life-threatening characteristics of AIDS, there is a great need to develop a general synthetic scheme for substituted 1,3-oxathiolanes which is efficient, amenable to large scale, inexpensive and based on readily available starting material. It is therefore an advantage of the present invention to provide synthesis of substituted 1,3-oxathiolanes that is readily feasible.

DESCRIPTION OF THE INVENTION

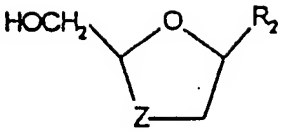
The processes of this invention may be used to prepare the compounds of formula (I) and pharmaceutically acceptable salts or esters thereof:



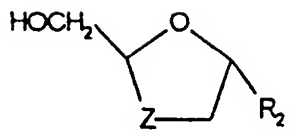
(I)

wherein R_2 is a purine or pyrimidine base or an analogue or derivative thereof; Z is S, S=O or SO_2.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centers (shown as * in formula (I)) and thus exist in the form of two pairs of optical isomers (i.e., enantiomers) and mixtures thereof including racemic mixtures. Thus the compounds of formula (I) may be either *cis* isomers, as represented by formula (II), or *trans* isomers, as represented by formula (III), or mixtures thereof. Each of the *cis* and *trans* isomers can exist as one of two enantiomers or as mixtures thereof including racemic mixtures. The preparation of all such isomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

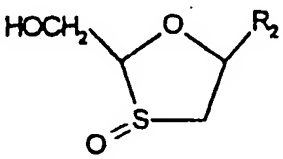


(II)

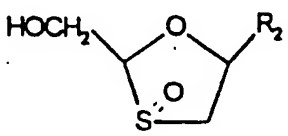


(III)

It will also be appreciated that when Z is S=O the compounds exist in two additional isomeric forms as shown in formulas (IIa) and (IIb) which differ in the configuration of the oxide oxygen atom relative to the 2,5-substituents. The processes of this invention additionally embrace the preparation of such isomers and mixtures thereof.



(IIa)



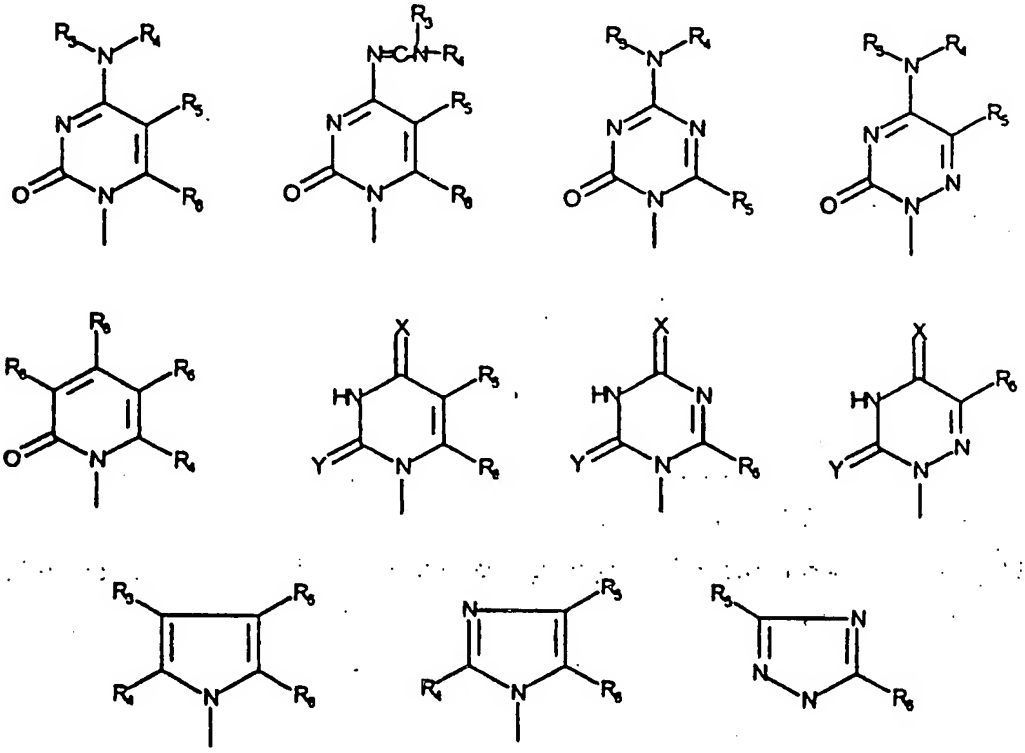
(IIb)

The purine or pyrimidine base or analogue or derivative thereof R_2 will be linked at any position of the base, preferably at the N9- or N1-position, respectively.

By "purine or pyrimidine base" or an analogue or derivative thereof is meant a purine or pyrimidine base found in native nucleosides or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the native bases but may either possess additional or lack certain of the functional properties of the native bases. Such analogues include those derived by replacement of a CH_2 moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice verse (for example 7-deazapurines, for example 7-deazadenosine or 7-deazaguanosine) or both (e.g., 7-deaza-8-azapurines). By derivatives of such bases or analogues are meant those compounds wherein ring substituents are either incorporated, removed or modified by conventional

substituents known in the art, e.g., halogen, hydroxyl, amino, C_{1-6} alkyl. Such purine or pyrimidine bases, analogues and derivatives will be well known to those skilled in the art.

Conveniently the group R_2 is selected from:

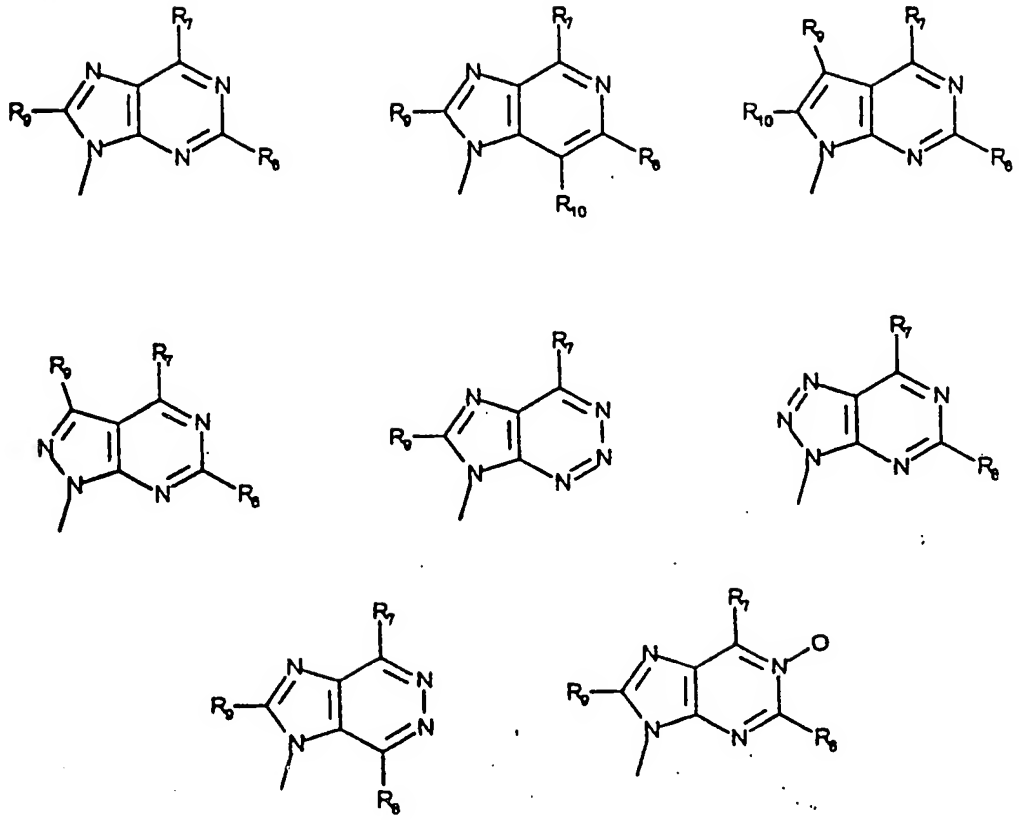


wherein:

X is oxygen or sulfur; Y is oxygen or sulfur;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, substituted or unsubstituted C_{1-6} alkyl, or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyl or aracyl;

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, cyano, carboxy, carbamoyl, alkoxycarbonyl (e.g. CO_2R_4), hydroxymethyl, trifluoromethyl, thioaryl, substituted or unsubstituted C_{1-6} alkyl or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyloxy;
and

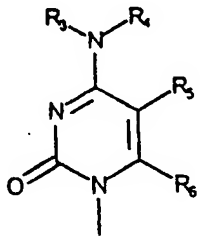


wherein:

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, alkoxy (e.g. OR_3), thiol, thioalkyl (e.g. SR_3), amino, substituted amino (e.g. NR_3R_4), halogen, cyano, carboxy, alkoxycarbonyl (e.g. CO_2R_3), carbamoyl, substituted or unsubstituted C_{1-6} alkyl, or alkenyl, or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy; and

R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxyl, alkoxy (e.g. OR_3), amino, substituted amino (e.g. NR_3R_4), halogen, azido, substituted or unsubstituted C_{1-6} alkyl or alkenyl or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy.

Preferably R_2 is



wherein R_3 and R_6 are hydrogen, and R_4 and R_5 are as defined above.

Z is preferably -S-.

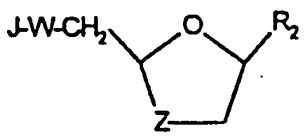
By "a pharmaceutically acceptable salt or ester" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety, R_2, and at the hydroxymethyl group of the oxathiolane ring. Modification at all such functional groups is included within the scope of the processes of this invention. However, of particular interest are pharmaceutically acceptable derivatives (e.g., esters) obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

Preferred esters of the compounds of formula (I) produced by the process of this invention include the compounds in which OH is replaced by a carboxyl function R(CO)O- in which the non-carbonyl moiety R is selected from hydrogen; straight or branched chain alkyl (e.g. methyl, ethyl, n-propyl, t-butyl, n-butyl); alkoxyalkyl (e.g. methoxymethyl); aralkyl (e.g. benzyl); aryloxyalkyl (e.g. phenoxymethyl); aryl (e.g. phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); substituted dihydropyridinyl (e.g. N-methyldihydropyridinyl); sulphonate esters such as

alkyl-or aralkylsulphonyl (e.g. methanesulphonyl); sulfate esters; amino acid esters (e.g. L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters. Also included within the scope of such esters are esters derived from polyfunctional acids such as carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids $HOOC(CH_2)_qCOOH$ where q is an integer of 0 to 10 (for example, succinic acid) or phosphoric acids.

Methods for preparing such esters are well known. See, for example, Hahn et al., "Nucleotide Dimers as anti-Human Immunodeficiency Virus Agents", Nucleotide Analogues, pp. 156-159 (1989) and Busso et al., "Nucleotide Dimers Supress HIV Expression In Vitro", AIDS Research and Human Retroviruses, 4(6), pp.449-455 (1988). Where esters are derived from such acids, each acidic group is preferably esterified by a compound of formula (I) or other nucleoside or analogs and derivatives thereof to provide esters of the formula:



(IV)

where W is $-OC-(CH_2)_n-CO-$ where n is an integer of 0 to 10, a phosphate group, or a thiophosphate group,

J is any nucleoside or nucleoside analog or derivative thereof and Z and R_2 are as defined above. Among the preferred nucleosides and nucleoside analogs are 3'-azido-2',3'-dideoxythymidine; 2',3'-dideoxycytidine; 2',3'-dideoxyadenosine; 2',3'-dideoxyinosine; 2',3'-dideoxythymidine; 2',3'-dideoxy-2',3'-didehydrothymidine; 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin and those nucleosides whose bases are depicted on pages 7-8 of this

specification. The most preferred dimer is a homodimer consisting of two nucleosides of formula (I).

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, preferably 1 to 4 carbon atoms and could contain one or more double bonds. Any aryl moiety present in such esters advantageously comprises a phenyl group.

In particular, the esters may be a C_{1-16} alkyl ester, an unsubstituted benzoyl ester or a benzoyl esters substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C_{1-6} alkyl or alkenyl, saturated or unsaturated C_{1-6} alkoxy, nitro or trifluoromethyl groups.

Pharmaceutically acceptable salts of the compounds of fomrula (I) include those derived from pharmaceutically acceptable inorganic and organis acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, *p*-toluenesulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and $NR4^+$ (where R is C_{1-4} alkyl) salts.

In the processes for preparing the compounds of this invention, the following definitions are used:
R_1 is a hydroxyl protecting function such as an acyl having from 1 to 16 carbon atoms unsubstituted or substituted with a heteroatom (e.g. benzoyl), or a silyl function such as trialkylsilyl (e.g. t-butyldimethylsilyl);
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;
R_w is hydrogen or R_1;
R_x is a substituted or unsubstituted C_{1-6} alkyl;
R_y is a substituted or unsubstituted C_{1-12} alkyl or substituted or unsubstituted C_{6-20} aryl; and
L is a leaving group.

As used in the processes of this invention, a "leaving group" is an atom or group which is displaceable upon reaction with an appropriate base, with or without a Lewis acid. Suitable leaving groups include alkoxy carbonyl groups such as ethoxy carbonyl; halogens such as iodine, bromine or chlorine, fluorine; substituted or unsubstituted saturated or unsaturated thiolates, such as thiomethyl or thiophenyl; substituted or unsubstituted saturated or unsaturated selenino compounds, such as phenyl selenide or alkyl selenide; substituted or unsubstituted saturated or unsaturated aliphatic or aromatic ketones such as methyl ketone; or -OR where R is hydrogen or a substituted or unsubstituted saturated or unsaturated alkyl group, e.g., a C_{1-6} alkyl or alkenyl group such as methyl; a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C_{1-6} aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl; a substituted or unsubstituted saturated or unsaturated alkoxy carbonyl group, such as methyl carbonate and phenyl carbonate; substituted or unsubstituted sulphonyl imidazolide; substituted or unsubstituted carbonyl

imidazolide; substituted or unsubstituted aliphatic or aromatic amino carbonyl group, such as phenyl carbamate; substituted or unsubstituted alkyl imidate group such as trichloroacetamidate; substituted or unsubstituted saturated or unsaturated phosphinoyl, such as diethylphosphinoyl; substituted or unsubstituted aliphatic or aromatic sulphonyl group, such as tosylate.

One process according to the invention is illustrated in SCHEME 1. The process of SCHEME 1 using specific reagents and compounds is depicted, for example, in SCHEMES 1A and 1B.

The various steps involved in the synthesis as illustrated in SCHEME 1 may be briefly described as follows:

Step 1: A mercaptoacetaldehyde monomer produced from the dimer in a suitable solvent is reacted directly with any aldehyde of the formula R_wOCH_2CHO (VII) to yield an oxathiolane lactol of formula (XIII).

Alternatively, the glycoaldehyde derivative of formula (VII) may be generated from the dimer by any means known in the art.

Step 2: The hydroxyl group of the compound of formula (XIII) is converted to a leaving group with a suitable reagent in a compatible organic solvent to yield an important oxathiolane intermediate of formula (XIV).

Step 3: The oxathiolane intermediate of formula (XIV) is reacted with a previously silylated purine or pyrimidine base to give a purin-9'-yl or pyrimidin-1'-yl substituted oxathiolane of formula (IX) where Z is sulfur. The compounds of formula (IX) are often predominantly obtained in the *cis* isomer.

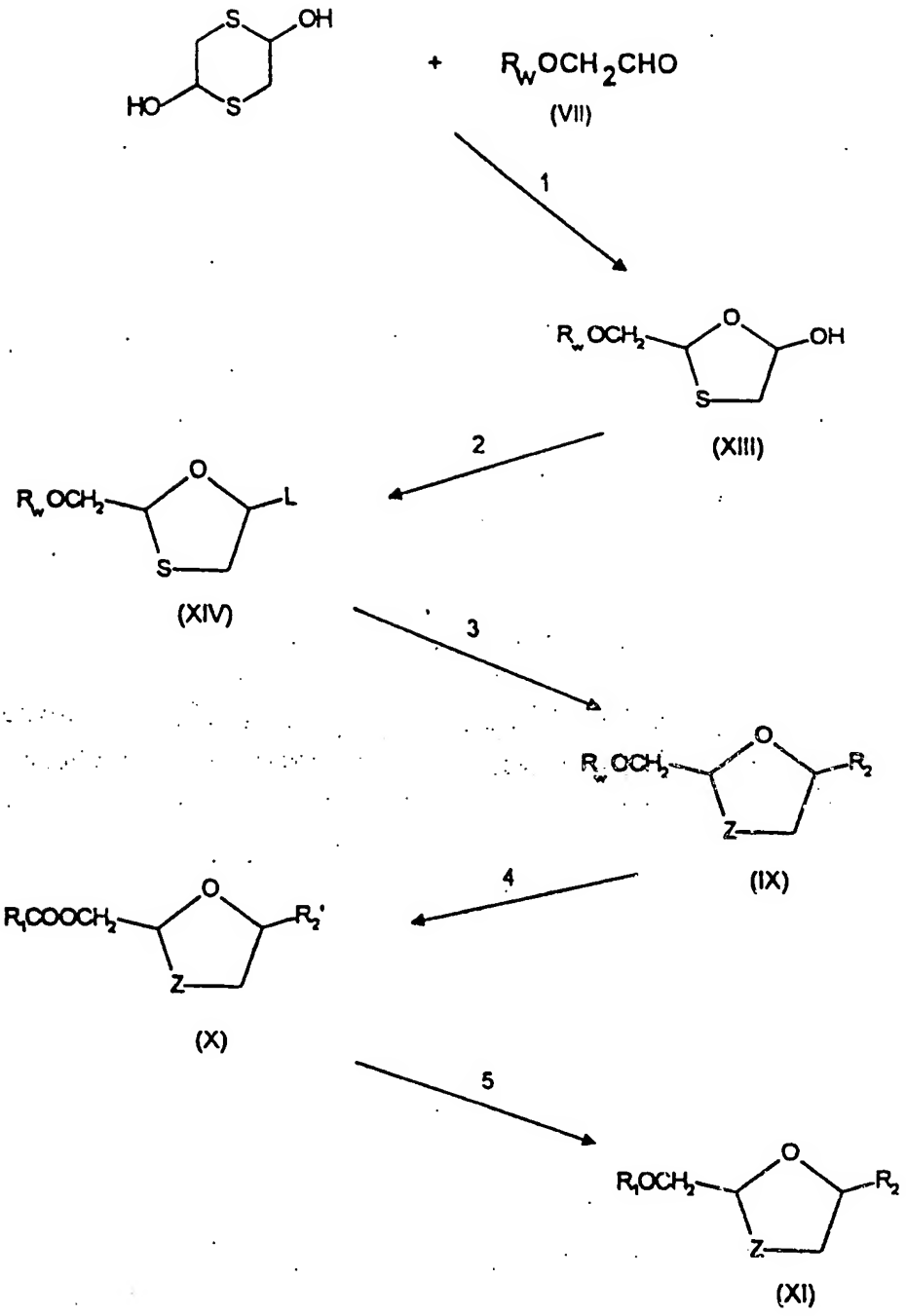
Optionally, the sulfur may be oxidized at this stage or at any other following stage to obtain compounds where Z is S=O or SO_2.

Step 4: The base R_2 shown in formula (IX) is acylated with acetic anhydride in a suitable solvent to yield a compound of formula (X) where R_2' is acylated R_2 which provides for easier separation of isomers.

Therefore, at this stage, the compound of formula (X) is optionally separated to its *cis* or *trans* isomer.

Step 5: The acetyl functionality of R_2' of compound of formula (X) are hydrolyzed under basic conditions to yield an oxathiolane of formula (XI).

Scheme 1


S
OH
HO
S
+
R_wOCH_2CHO
(VII)
1
R_wOCH_2
O
OH
S
(XIII)
2
R_wOCH_2
O
L
S
(XIV)
3
R_wOCH_2
O
R_2
Z
(IX)
4
R_1COOCH_2
O
R_2'
Z
(X)
5
R_1OCH_2
O
R_2
Z
(XI)

Scheme 1a:

Step 1: A mercaptoacetaldehyde monomer produced from the dimer in pyridine is reacted directly with benzoyloxyacetaldehyde (VII-A) to yield an oxathiolane lactol of formula (XIII-A).

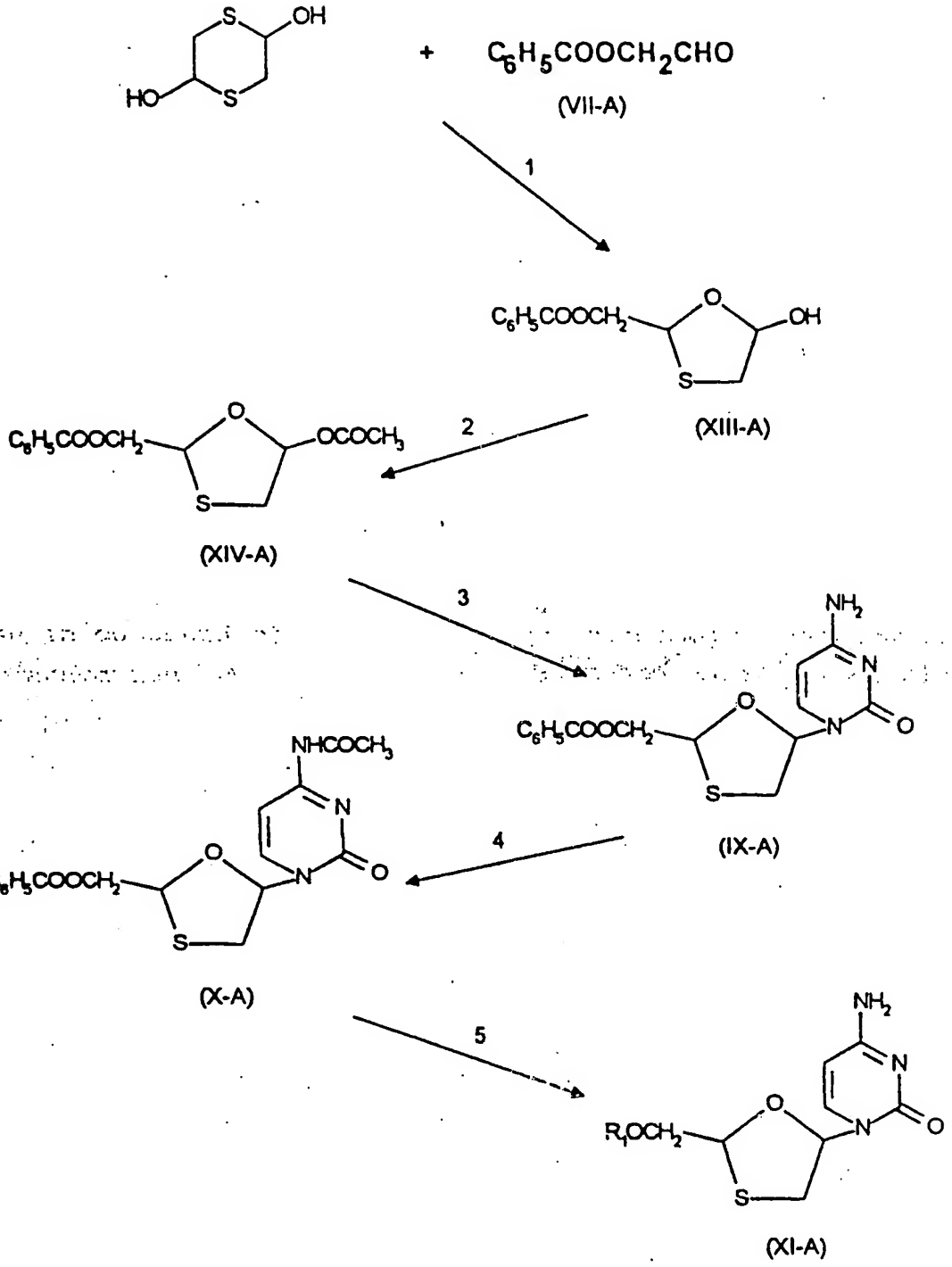
Step 2: The hydroxyl group of the compound of formula (XIII-A) is converted to a leaving group with acetyl chloride in a compatible organic solvent to yield intermediate of formula (XIV-A).

Step 3: The oxathiolane intermediate of formula (XIV-A) is reacted with a previously silylated cytosine to give a cytosin-1'-yl oxathiolane of formula (IX-A) where Z is sulfur.

Step 4: The amine function of the base in compound of formula (IX-A) is acylated with acetic anhydride in pyridine to yield a compound of formula (X-A) which provides for easier separation of isomers.

Step 5: The N-acetyl function of the compound of formula (X-A) are hydrolyzed under basic conditions to yield an oxathiolane of formula (XI-A).

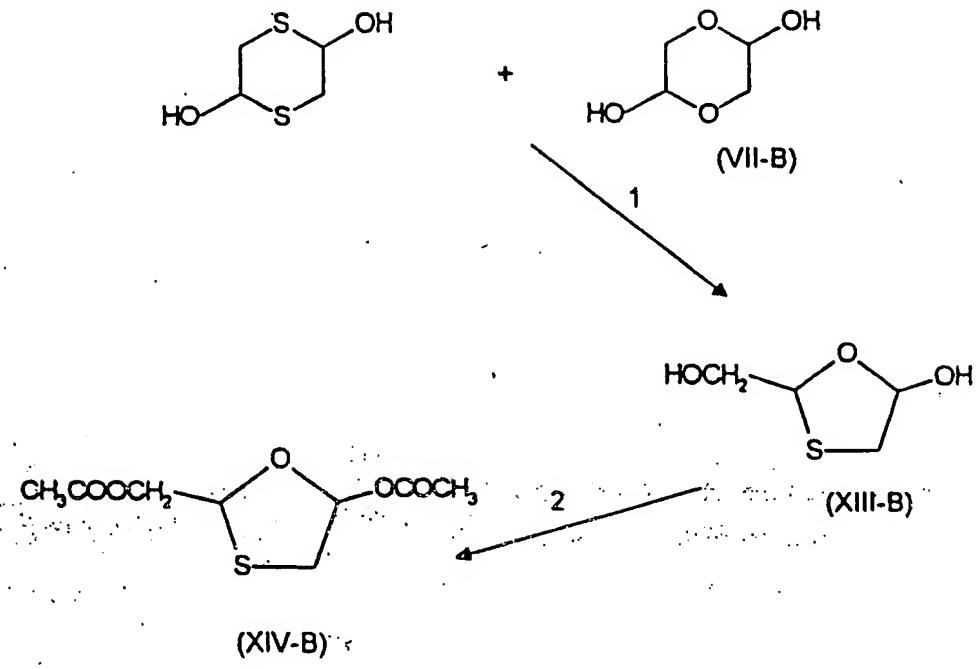
Scheme 1a



Scheme 1b:

The glycoaldehyde dimer (VII-B) is used as a source of the glycoaldehyde.

Scheme 1b



A second and preferred process for producing oxathiolane compounds is illustrated in SCHEME 2. This process is illustrated using specific reagents and compounds in SCHEME 2A.

The various steps involved in the synthesis as illustrated in SCHEME 2 may be briefly described as follows:

Step 1: Mercaptoacetaldehyde monomer produced from the dimer in a suitable solvent is reacted directly with any organic glyoxylate of the formula $R_yOOCCHO$ to yield an oxathiolane lactol of formula (XV).

Step 2: The hydroxyl group of the compound of formula (XV) is converted to a leaving group with a suitable reagent in a compatible organic solvent to yield an important oxathiolane intermediate of formula (XVI).

Step 3: The oxathiolane intermediate of formula (XVI) is reacted with a previously silylated purine or pyrimidine base, in the presence of a Lewis acid, to give purin-9'-yl or pyrimidinyl-1'-yl substituted oxathiolane of formula (XVII) where Z is S, predominantly as the *cis*-isomer.

Optionally, the sulfur may be oxidized at this stage or at any other following stage to give compounds where Z is S=O or SO_2.

Step 4: The ester group of the oxathiolane of formula (XVII) is selectively reduced with a suitable reducing agent in a compatible organic solvent to yield an oxathiolane nucleoside of formula (XVIII).

At this stage, the compound of formula (XVIII) is optionally separated to its *cis* and *trans* isomers.

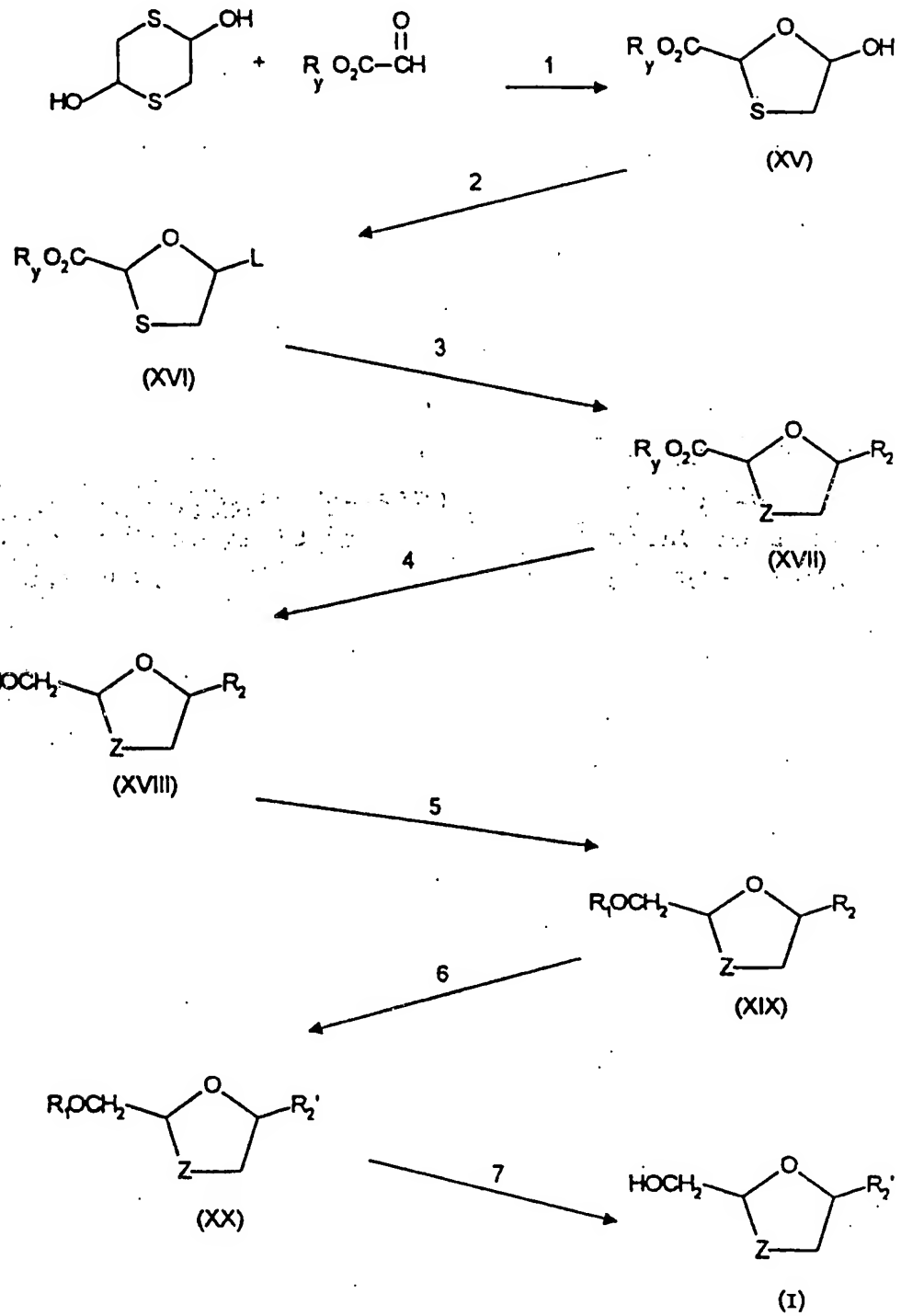
Step 5: The hydroxyl group of the compound of formula (XVIII) is protected with a suitable silyl protecting group in an appropriate solvent to yield an oxathiolane of formula (XIX).

Step 6: The R_2 base of formula (XIX-A) can be interconverted to another base R_2' by reaction with a suitable reagent to yield an oxathiolane of formula (XX).

Step 7: The protecting group R_1 of the compound of formula (XX) is removed under neutral conditions using a

suitable reagent in a suitable solvent to yield the oxathiolane of formula (I).

Scheme 2



Scheme 2a:

Step 1: Mercaptoacetaldehyde dimer in pyridine is reacted directly with ethyl glyoxylate to yield an oxathiolane lactol of formula (XV-A).

Step 2: The hydroxyl group of the compound of formula (XV-A) is converted to an acetal leaving group with acetyl chloride in a compatible organic solvent to yield intermediate of formula (XVI-A).

Step 3: The oxathiolane intermediate of formula (XVI-A) is reacted with previously silylated uracil, in the presence of trimethylsilyl iodide, to give uracil-1'-yl oxathiolane of formula (XVII-A), predominantly as the *cis*-isomer.

Step 4: The ester group of the oxathiolane of formula (XVII-A) is selectively reduced with sodium borohydride in methanol to yield an oxathiolane nucleoside of formula (XVIII-A).

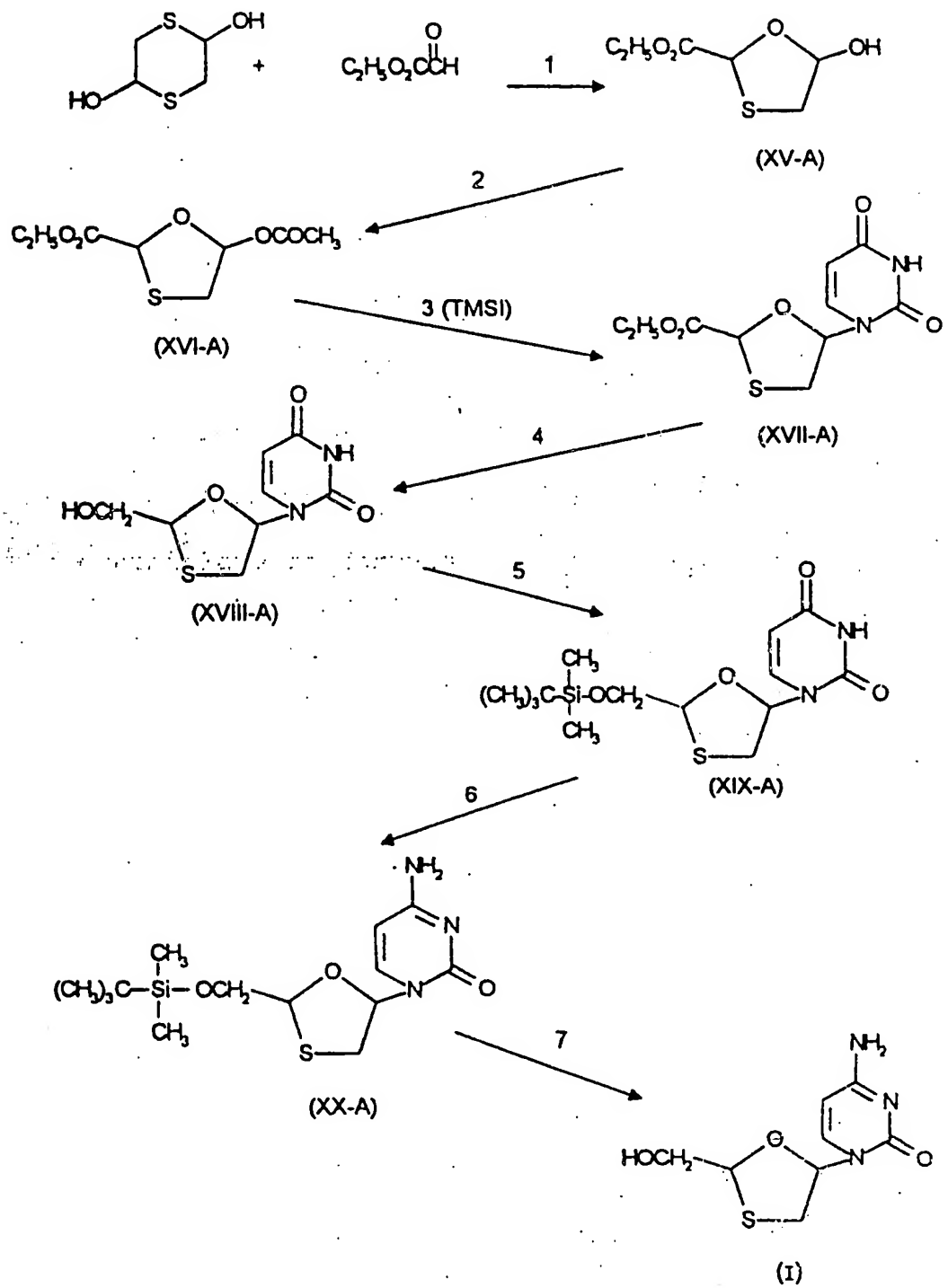
Step 5: The hydroxyl group of the compound of formula (XVIII-A) is protected with t-butyldimethyl silyl in dimethylformamide (DMF) to yield an oxathiolane of formula (XIX-A).

Step 6: The uracil base of formula (XIX-A) can be interconverted to cytosine, by reaction with p-chlorophenoxy phosphorous oxychloride followed by amination with ammonia in methanol to yield an oxathiolane of formula (XX-A).

Step 7: The silyl group of the compound of formula (XX-A) is removed under neutral conditions using tetra n-

butyl ammonium fluoride in tetrahydrofuran to yield the oxathiolane of formula (I).

Scheme 2a

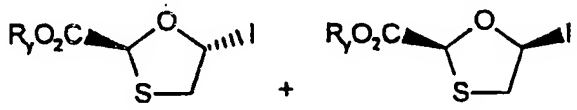


Although the process of Scheme 2 generally provides nucleoside analogues predominantly in their *cis* form, such a process is most preferred for pyrimidine bases because of high *cis*-selectivity.

For purines, although the process of Scheme 2 does yield more *cis* isomer than *trans*, the ratio obtained is moderate. An alternative process has been designed to obtain purin-yl nucleosides in high *cis*:*trans* ratios.

Briefly, steps 1 and 2 of Scheme 2 remain the same. However, the coupling procedure (step 3) between the compound of formula (XVI) and the base (preferably purine) is modified as follows:

Step 3a: The oxathiolane intermediate of formula (XVI) is reacted with a halogen-containing silyl Lewis acid such as trimethylsilyl iodide, to give an intermediate of formula (XXVI):



(XXVI)

which is the iodo ester of the intermediate of formula (XVI).

Step 3b: The intermediate of formula (XXVI) is then mixed with a base (preferably a purine) under basic conditions to yield the intermediate of formula (XVII) predominantly as the *cis* isomer.

As an alternative to process 2, a third process according to this invention for producing oxathiolane compounds is illustrated in SCHEME 3. This process is illustrated using specific reagents and compounds, for example, in SCHEME 3A.

The various steps involved in the synthesis as illustrated in SCHEME 3 may be briefly described as follows:

Step 1: Similar to Scheme 2.

Step 2: The hydroxyl group of the intermediate of formula (XV), is converted to a leaving group with a suitable reagent in a compatible organic solvent to yield an important intermediate of formula (XXI).

Step 3': The ester group of the intermediate of formula (XXI) is selectively reduced with a suitable reducing agent in a compatible organic solvent and the resultant hydroxyl group is directly protected with a suitable group R_1 to yield an oxathiolane of formula (XXII).

Step 4': The oxathiolane of formula (XXII) is reacted with previously silylated purine or pyrimidine base in the presence of a Lewis Acid to give a pyrimidin-1'-yl or purin-9'-yl oxathiolane of formula (XXIII) where Z is S (and optionally oxidized to S=O or SO_2).

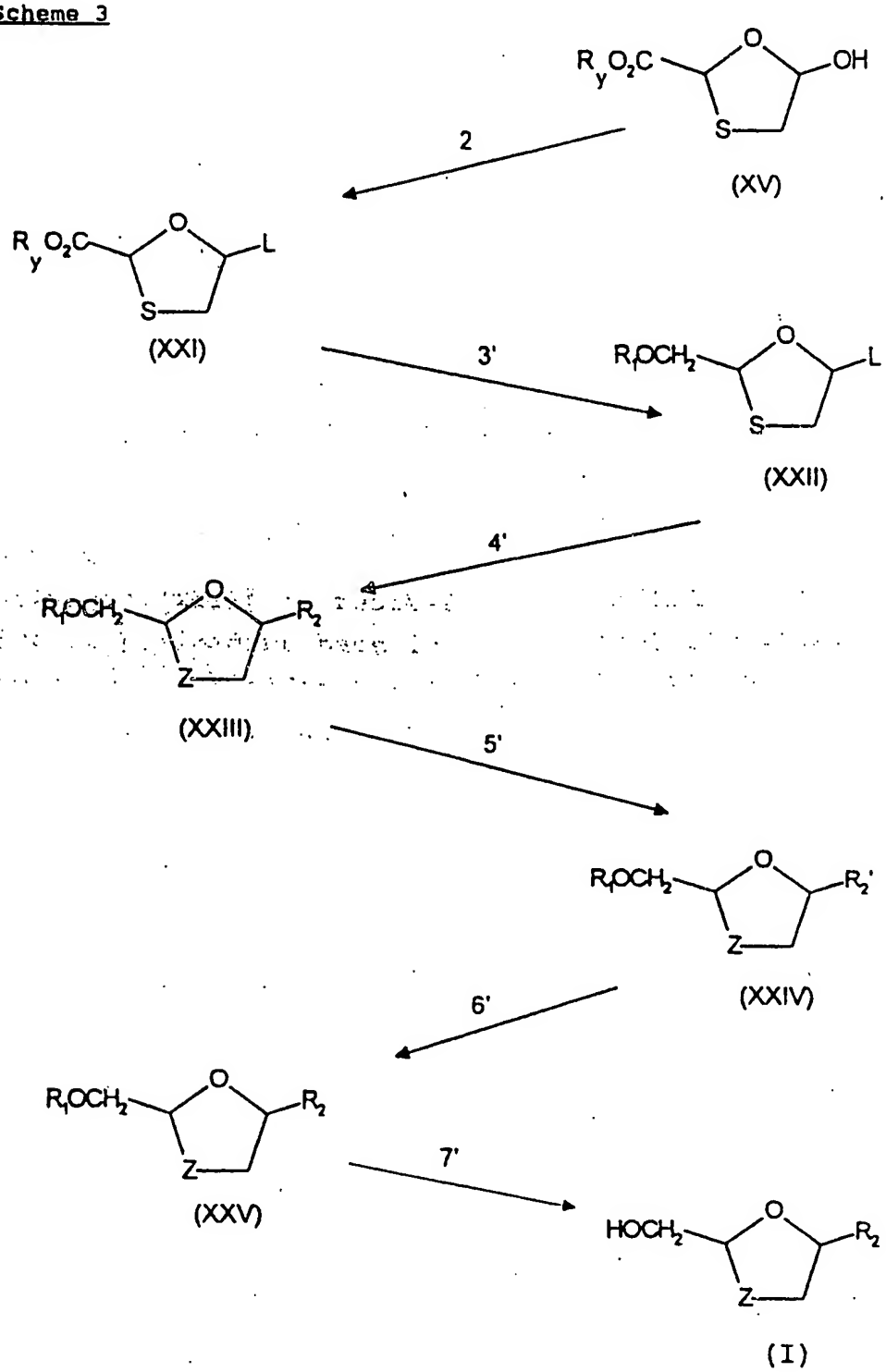
Step 5': The base R_2 shown in formula (XXIII) is acylated with acetic anhydride in a solvent to yield a compound of formula (XXIV) where R_2' is an acylated R_2 which provides for easier separation of isomers.

Therefore, at this stage, the compound of formula (X) is optionally separated to its *cis* or *trans* isomer.

Step 6': The acetyl functionality of the compound of formula (XXIV) is hydrolyzed under basic conditions to yield an oxathiolane of formula (XXV).

Step 7': Removal of the R_1 protecting group is effected by suitable reagents in a compatible solvent to yield an oxathiolane of formula (I).

Scheme 3



Scheme 3a:

Step 2: The hydroxyl group of the intermediate of formula (XV-A), is converted to an acetal leaving group with methyl chloroformate in a compatible organic solvent to yield intermediate of formula (XXI-A).

Step 3': The ester group of the intermediate of formula (XXI-A) is selectively reduced with sodium borohydride in methanol and the resultant hydroxyl group is directly protected with t-butyldiphenylsilyl to yield an oxathiolane of formula (XXII-A).

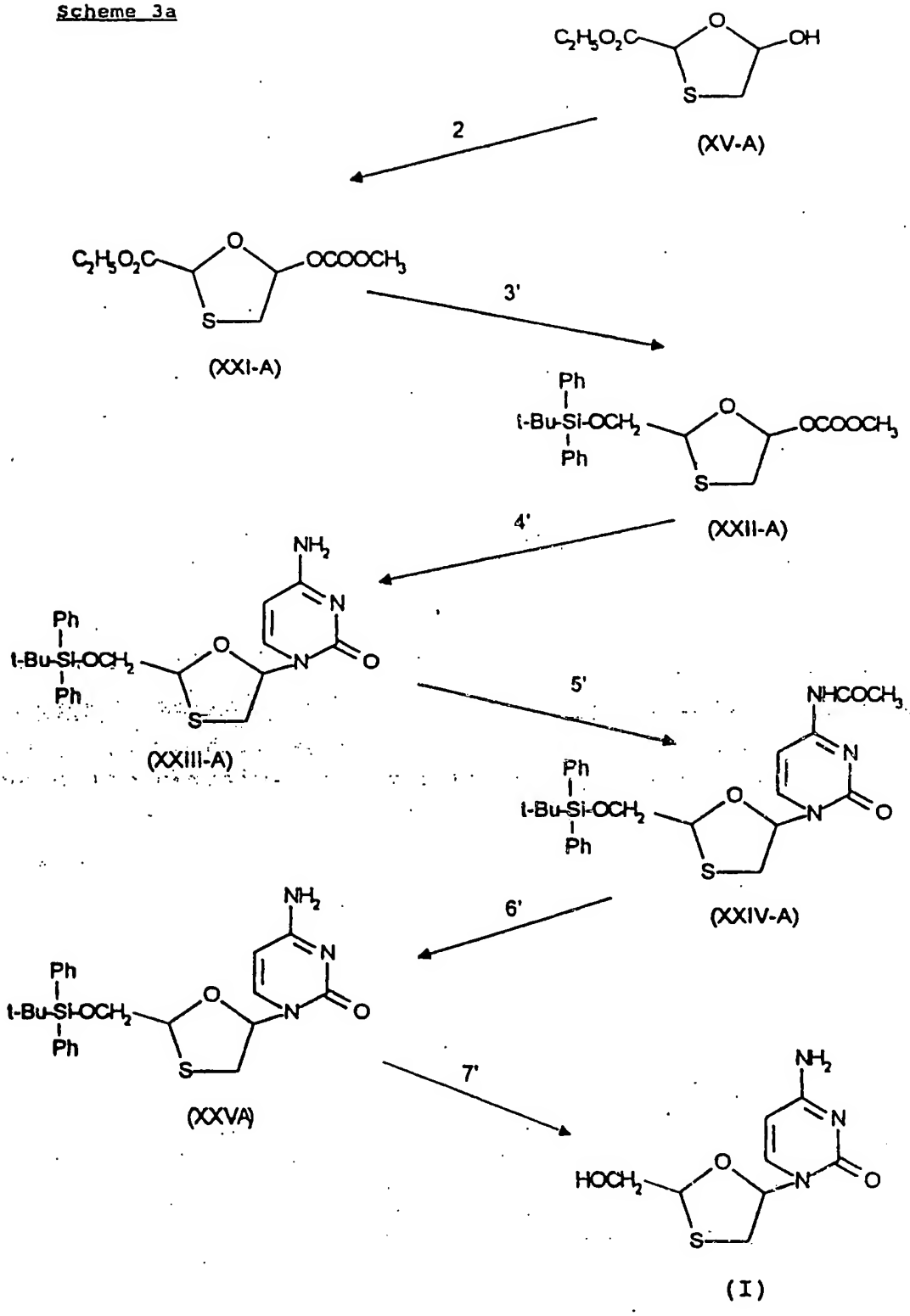
Step 4': The oxathiolane of formula (XXII-A) is reacted with previously silylated cytosine, in the presence of trimethylsilyltriflate or iodotrimethylsilane, to give cytosin-1'-yl oxathiolane of formula (XXIII-A).

Step 5': The amine function of the cytosine of compound (XXIII-A) is acylated with acetic anhydride in pyridine to yield a compound of formula (XXIV-A) so that the *cis*- and *trans*-isomers may be separated.

Step 6': The acetyl functionality of the compound of formula (XXIV-A) is hydrolyzed under basic conditions to yield an oxathiolane of formula (XXV-A).

Step 7': Removal of the silyl group is effected by using tetra-n-butylammonium fluoride in tetrahydrofuran yield an oxathiolane of formula (I).

Scheme 3a



In the processes of this invention, the following intermediates are of particular importance:
trans-2-hydroxymethyl-5-acetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(4',5'-dichlorobenzoyloxy)-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-trimethylacetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(2',2',2'-trichloroethoxycarbonyloxy)1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-ethoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-methoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-acetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(N4'-acetylcytosin-1'-yl)-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-hydroxy-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-methoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-acetoxy-1,3-oxathiolane;
cis-2-carboethoxy-5-(N4'-acetylcytosin-1'-yl)-1,3-oxathiolane;
cis-2-carboethoxy-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis-2-carboethoxy-5-(uracil-1'-yl)-1,3-oxathiolane;
cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis- and *trans*-ethyl-5-iodo-1,3-oxathiolan-2-carboxylate;
cis- and *trans*-ethyl-5-(6'-chloropurin-9'-yl)-1,3-oxathiolan-2-carboxylate; and

cis- and *trans*-ethyl-5-(6'-chloropuin-7'-yl)-1,3-oxathiolan-2-carboxylate.

Some of the steps described hereinabove have been reported in the context of purine nucleoside synthesis, for example, in "Nucleoside Analogues - Chemistry, Biology and Medical Applications", R.T. Walker et al., Eds, Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated herein by reference.

It will be appreciated that the reactions of the above described processes may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1991). Examples of suitable hydroxyl protecting groups include groups selected from aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under

acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by hydrogenolysis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes the compounds of formula (I) are generally obtained as a mixture of the *cis* and *trans* isomers. However, in the process depicted in Scheme 2, the ratio of *cis*:*trans* may approach 15:1 for pyrimidines, whereas it may approach 10:1 for the purines in the case of the modified process of Scheme 2.

These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base

with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as $POCl_3$, or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

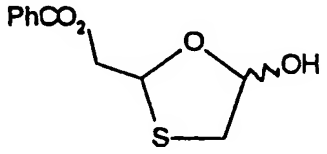
Examples 1 to 7, and 19 to 23 relate to the process as depicted in Scheme 1. Examples 8 to 10, and 13 to 18 relate to the process as depicted in Scheme 2, and Examples 11, 12, and 19 to 21 relate to the process as depicted in Scheme 3. Examples 24 and 25 relate to the

modified process as depicted in Scheme 2 (preferably for purines) and summarized on page 20 of this application.

EXAMPLES.

EXAMPLE 1

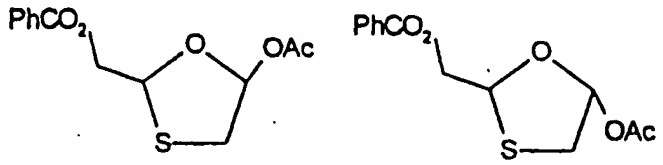
CIS AND *TRANS* 2-BENZOYLOXYMETHYL-5-HYDROXY -1,3-OXATHIOLANE



A solution of 216.33 g (1.32 mol) of benzoyloxyacetaldehyde and 100.31 g (0.66 mol) of 1,4-dithiane-2,5-diol in 373 ml (4.61 mol) of pyridine was heated at 60-65°C under nitrogen atmosphere for 1 hour until all solids dissolved. After cooling, pyridine was removed by distillation and the residue was purified on a silica gel column using EtOAc: hexanes (1:2) as eluent to give 268.5 g of the title compounds (2:1 *trans:cis*); ^{1}H NMR ($CDCl_3$) δ 3.03 (m, CH_2S), 4.40 (m, CH_2O), 4.70 (brs, 0.66H), 4.83 (brs, 0.33H), 5.45 (m, 0.33H), 5.62 (t, 0.66H, J=5Hz), 5.73 (brs, 0.33H), 5.88 (brs, 0.,66H), 7.94 (d, 0.66H, J=7.3 Hz), 7.98 (d, 1.33H, J=7.3 Hz), 7.49 (t, 1H, J=7 Hz), 7.99 (d, 2H, J=7.3 Hz)
^{13}C NMR ($CDCl_3$) *trans* isomer δ 37.9, 65.9, 80.6, 99.6, 129.5, 129.3, 128.2, 133.0, 166.2;
cis isomer δ 38.5, 65.9, 82.1, 100.4, 128.3, 129.3, 133.0, 166.3.

EXAMPLE 2

CIS AND *TRANS* 2-BENZOYLOXYMETHYL-5-ACETOXY -1,3-OXATHIOLANE



To a solution of 29.76 g (0.132 mol) of *cis* and *trans* 2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane (as prepared in Example 1) in dichloromethane (65 mL) and pyridine (32 mL) was added dropwise 28.1 mL (0.395 mol) of acetyl chloride at 0 - 5° C over 1.5 to 2 hours. The reaction mixture was stirred at 0 - 5°C for 30 minutes then it was poured carefully onto a cold (0°C) solution of saturated sodium bicarbonate. The organic layer was separated and the water layer was extracted with dichloromethane (3 X 20 mL). The combined organic layers were washed with saturated sodium bicarbonate (3 X 20 mL) and brine (20 mL), and was dried over sodium sulfate. Following filtration, the solvents were removed *in vacuo* to give 32.1 g of crude product which was purified by Kugelrohr distillation or filtration through a short silica gel column (eluent hexanes: EtOAc 3:1). The purified product consisted of a 3:1 mixture of *trans* : *cis* isomers.

^{1}H NMR ($CDCl_3$)δ 2.09 (s, 0.75H), 2.10 (s, 2.25H), 3.22 (m, 2H), 4.54 (m, 2H), 5.68 (m, 1H), 6.64 (d, 0.25H, J=4.2Hz), 6.72 (d, 0.75H, J=4.1Hz), 7.45 (dd, 2H, J=7.6Hz), 7.55 (t, 1H, J=7.3 Hz), 8.05 (dd, 2H, J=7.4 Hz).

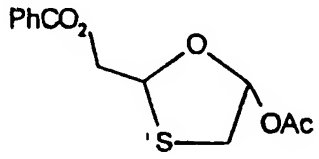
^{13}C NMR ($CDCl_3$) *trans* isomer δ 20.7, 37.3, 65.8, 83.1, 98.9, 128.2, 129.4, 129.5, 133.0, 165.7, 169.6.

Cis isomer δ 20.7, 37.9, 67.5, 84.4, 99.1, 128.2, 129.4, 129.5, 133.0, 165.7, 169.5.

The *trans* compound can be isolated by washing the mixture with ethanol and removing the solvent *in vacuo*.
m.p. 67 - 68°C
^{1}H NMR (DMSO- d_6) δ 2.10 (s, 3H), 3.18 (d, 1H), 3.39 (dd, 1H), 4.48 (d, 2H), 5.67 (d, 1H), 6.65 (d, 1H), 7.56 (m, 2H), 7.70 (m, 1H), 7.98 (m, 2H).

EXAMPLE 3

TRANS-2-BENZOYLOXYMETHYL-5-ACETOXY-1,3-OXATHIOLANE

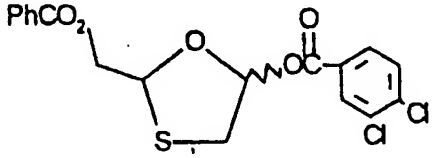


A solution benzoyloxyacetaldehyde (ca. 465 g) in toluene (ca. 2l) was treated with 1,4 -dithiane-2,5-diol (227.2 g, 1.49 mol) and the suspension was stirred and heated at 75 - 80°C for 5 hours. The mixture was cooled to 25 - 30°C and the remaining solid (unreacted dithiane) was collected by filtration.
The filtrate was diluted with pyridine (362 mL, 4.48 mol) and the resulting solution was cooled to 0 - 5°C. Acetyl chloride (316.8 mL, 4.46 mol) was added during 20 minutes such that the temperature was maintained in the range 0 - 20° and the mixture was then stirred at 27 - 30°C for 30 minutes. The reaction mixture was cooled to 5 - 10°C and 1M hydrochloric acid (1.91, 1.9 mol) was added such that the temperature was maintained in the range 5 - 20°C. The phases were separated and the aqueous phase was extracted with toluene (1.9l). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (2.8l). The organic was concentrated *in vacuo* at ca. 45°C to an oil. This oil was diluted with ethanol (IMS, 3l) and was reconcentrated to an oil. This was treated with ethanol (IMS, 2.5l), the mixture stirred at 0 - 5°C for 3.5 hours and the resultant suspension was stored at 2°C for

17 hours. The product was isolated by filtration to give the title compound as a cream coloured solid, 147.3 g; m.p. 67 - 68°C;
^1H NMR (DMSO-d_6): δ 7.98 (m, 2H, aromatic), 7.70 (m, 1H, aromatic), 7.56 (m, 2H, aromatic), 6.65 (d, 1H, C_5-H), 5.67 (d, 1H, C_2-H), 4.48 (d, 2H, CH_2-C_2), 3.39 (dd, 1H, C_4-H_2), 3.18 (d, 1H, C_4-H_2), 2.10 (s, 3H, OCO-CH_3).

EXAMPLE 4

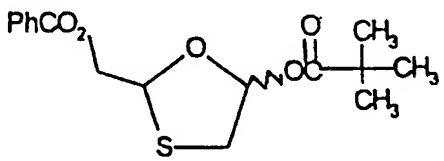
CIS AND *TRANS* 2-BENZOYLOXYMETHYL-5-(3',4'-DICHLOROBENZOYLOXY)-1,3-OXATHIOLANE



A mixture of *cis* and *trans* 2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane (as prepared in example 1) (8.99 g, 39.8 mmol) was reacted with 8.3 g (39.6 mmol) of 3,4-dichlorobenzoylchloride in dichloromethane (30 mL) and pyridine (9.6 mL) as described in Example 2 to yield 4.86 g of the desired compounds in 1:1 ratio .
^1H NMR ($CDCl_3$) δ 3.35 (m, 2H), 4.55 (m, 2H), 5.72 (m, 1H), 6.80 (m, 0.5H), 6.93 (m, 0.5H), 7.26 (d, 1H, J=6.8Hz), 7.38 (m, 1H), 7.82 (m, 2H)
^{13}C NMR ($CDCl_3$) δ, 37.4, 38.1, 65,9, 67.3, 83.5, 84.9, 100.1, 100.4, 128.5, 129.5, 129.6, 129.7, 129.8, 130.7, 131.7 ,133.1, 133.3, 133.4, 138.3, 163.5, 163.6 166.0, 166.2.

EXAMPLE 5

CIS AND *TRANS* 2-BENZOYLOXYMETHYL-5-TRIMETHYLACETOXY-1,3-OXATHIOLANE



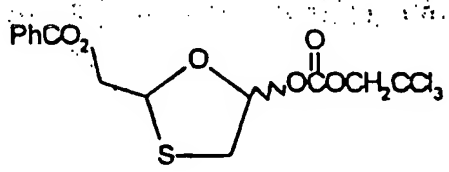
A mixture of *cis* and *trans* 2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane (8.9 g, 39.6 mmol) (as prepared in example 1) was reacted with 14.6 mL (118.8 mmol) of trimethylacetylchloride in dichloromethane (35 mL) and pyridine (9.6 mL) as described in example 2 to yield 7.94 g of the desired compound in 1:1 *ratio* .

^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 3.16 (dd, 1H), 3.30 (m, 1H), 4.50 (m, 2H), 5.60 (m, 1H), 6.65 (d, 0.5H, J=4.7Hz), 6.68 (d, 0.5H, J=4.1Hz), 7.43 (m, 2H), 7.53, (m, 1H), 8.05 (d, 2H, J=7.8Hz).

^{13}C NMR ($CDCl_3$) δ, 26.6, 37.3, 37.9, 38.4, 38.7, 66.0, 68.1, 83.1, 84.5, 99.2, 99.7, 128.5, 129.7, 129.8, 129.9, 133.3, 166.2, 177.4.

EXAMPLE 6

***CIS* AND *TRANS* 2-BENZOYLOXYMETHYL-5-(2',2',2'-TRICHLOROETHOXYCARBONYLOXY)-1,3-OXATHIOLANE**



A mixture of *cis* and *trans* 2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane 4.47 g (19.8 mmol) (as prepared in example 1) was reacted with 8.2 mL (59.4 mmol) of 2,2,2-trichloroethylchloroformate in pyridine (4.8 mL) and dichloromethane (150 mL) as described in example 2 to give 6.0 g of the title compound in 2:1 ratio .

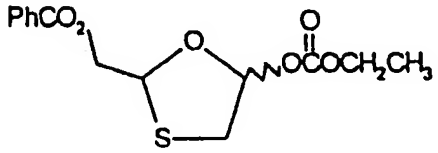
^{1}H NMR ($CDCl_3$) δ 3.32 (m, 2H), 4.74 (m, 2H), 4.80 (s, 2H), 5.71 (m, 1H), 6.55 (brs, 0.33H), 6.62 (d, 0.66H), 7.41 (dd, 2H), 7.53 (t, 1H), 8.00 (d, 2H).

^{13}C NMR ($CDCl_3$) *trans* isomer δ 37.0, 65.6, 77.0, 83.6, 93.8, 102.9, 128.4, 129.6, 129.7, 133.3, 133.4, 153.1, 165.8.

Cis isomer δ 37.6, 67.6, 85.0, 93.9, 102.9, 128.4, 129.6, 129.7, 133.3, 152.6, 165.8.

EXAMPLE 7

CIS AND *TRANS*-2-BENZOYLOXYMETHYL-5-ETHOXYCARBONYLOXY -1,3- OXATHIOLANE



A mixture of *cis* and *trans* 2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane 1.49 g (6.6 mmol) (as prepared in Example 1) was reacted with ethylchloroformate 1.3 mL (13.2 mmol) and pyridine (3.3 mL) as described in example 2 to give 1.51 g of the title compound.

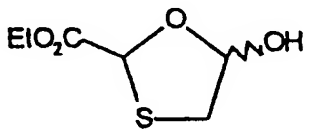
^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J=6.5 Hz), 3.16 (m, 2H), 4.10 (q, 2H, J=6.5), 4.43 (m, 2H), 5.61 (m, 1H), 6.45 (d, 0.33H, J=3.5 Hz), 6.54 (d, 0.66H, J=4.1, Hz), 7.36 (dd, 2H, J=7.4 Hz), 7.46 (t, 1H, 7.6 Hz), 7.95 (d, 2H, J=7.2 Hz).

^{13}C NMR ($CDCl_3$) *trans* δ 13.4, 36.7, 63.7, 65.5, 82.9, 101.6, 129.3, 129.4, 128.1, 132.8, 153.4, 165.6

cis δ 13.4, 37.3, 63.7, 67.0, 84.3, 101.7, 129.3, 129.4, 128.1, 132.8, 153.3, 165.6.

EXAMPLE 8

CIS AND *TRANS*-2-CARBOETHOXY-5-HYDROXY-1,3-OXATHIOLANE



A mixture of the mercaptoacetaldehyde dimer (5.1 g, 33.65 mmol), ethyl glyoxylate (8.58 g, 2.5 equivalents), and a magnetic stirring bar were placed in a round bottom flask. After flushing with argon, the mixture was heated with a heat gun with stirring until a pale yellow oil was obtained (about 3 to 5 minutes). The

crude product was then purified by flash column chromatography (45% ethyl acetate in hexanes) to give the desired material (7 g, 58% yield) as a mixture of isomers epimeric at C-5.

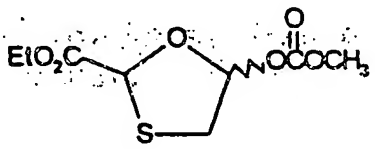
Note:Ethyl glyoxylate was prepared according to the procedure reported by T.R. Kelly and coworkers [Synthesis, 544 (1972)].

^1H NMR ($CDCl_3$) δ 1.30 (m, 3H), 3.11 (m, 2H), 4.21 (m, 2H), 5.56 (s, 0.5H), 5.59 (s, 0.5H), 5.89 (m, 0.5H), 6.02 (m, 0.5H)

^{13}C NMR ($CDCl_3$) δ 13.7, 38.2, 40.0. 61.8, 62.5, 77.7, 79.8, 101.3, 103.0, 170.1.

EXAMPLE 9

CIS AND *TRANS* 2-CARBOETHOXY-5-METHOXYCARBONYLOXY-1,3-OXATHIOLANE



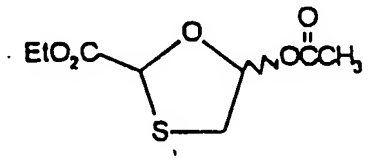
To a cold (-25°C) stirred solution of the crude hydroxy compound (10 g) (as prepared in example 8) and pyridine (9.1 mL, 0.113 mmol) in dry dichloromethane (20 mL) under argon was added methyl chloroformate (8.7 mL, 0.113 mmol) slowly over a period of 5 minutes. Upon completion of addition, the cooling bath was removed and the reaction mixture was stirred for 3 hours. Water (20 mL) was added to the mixture and stirring was continued for another 5 minutes. The resulting mixture was diluted with dichloromethane (150 mL) and washed with 1 M HCl (3 x 40 mL), saturated sodium bicarbonate (40 mL), brine (40 mL), and then was dried over sodium sulphate. Removal of the solvent under reduced pressure gave 9.2 g of the crude product which was purified by flash column chromatography (25% ethyl acetate in hexanes). The *trans* carbonate was obtained in pure form (4.02 g), as

indicated by the NMR spectrum of the material. However, an additional 1.65 g was obtained and found to be contaminated with the *trans* compound (20%) as determined by NMR integration.

^{1}H NMR ($CDCl_3$) *trans* δ 1.29 (t, 3H, J=7.1 Hz), 3.24 (d, 1H, J=11.9 Hz), 3.44 (d of d, 1H, J=4.1, 11.9 Hz), 3.82 (s, 3H), 4.24 (q, 2H, J=7.1 Hz), 5.65 (s, 1H), 6.69 (d, 1H, J=4.1 Hz).

EXAMPLE 10

CIS AND *TRANS* 2-CARBOETHOXY-5-ACETOXY-1,3- OXATHIOLANE



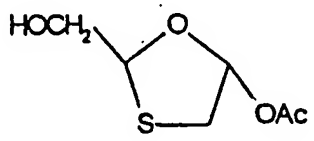
To a cold (0°C) stirred solution of the hydroxy compound (6.0 g, 33.7 mmol) obtained as in Example 8, and pyridine (5.45 mL) in dry dichloromethane (25 mL) under argon was added slowly acetyl chloride (3.60 mL, 1.5 equivalents) over a period of 20 minutes. The resultant mixture was stirred for 1 hour and 45 minutes. Analysis of the reaction mixture by TLC showed that all starting material was consumed. The excess acetyl chloride was quenched by the addition of methanol (2 mL). The mixture was diluted with ether (150 mL) and was washed with water (3 X 40 mL), 1 M HCL (40 mL) saturated sodium bicarbonate (40 mL), and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave 4.67 g of the crude product. The combined aqueous washings was extracted with ethyl acetate (3 x 50 mL). Concentration of the extract provided another 1 g of the crude product. The combined crude product was subjected to flash column chromatography (25% ethyl acetate in hexanes) to afford 2.2 g of the *trans* acetate (the less polar component). The corresponding *cis*

acetate was obtained as a mixture (1.71 g) contaminated with small amount of the *trans* isomer.

^{1}H NMR ($CDCl_3$) *trans* δ 1.30 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 3.17 (d, 1H, J=11.8 Hz), 3.44 (dd, 1H, J=9, 11.8 Hz), 4.25 (q, 2H, J=7.1 Hz), 5.65 (s, 1H), 6.80 (d, 1H, J=4.0 Hz).

EXAMPLE 11

TRANS-2-HYDROXYMETHYL-5-ACETOXY-1,3-OXATHIOLANE

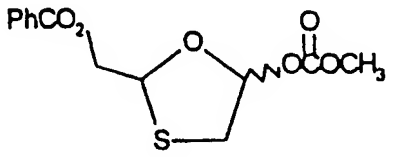


Sodium borohydride (27 mg, 0.708 mmol) was added to a magnetically stirred solution of *trans*-2-carboethoxy-5-acetoxy-1,3-oxathiolane (52 mg, 0.236 mmol) in methanol (1 mL) at 0°C under an argon atmosphere. The resultant solution was stirred for 25 minutes at 0°C. The reaction was quenched with 2 drops of saturated ammonium chloride solution followed by dilution with diethyl ether (4 mL). This mixture was stirred at room temperature for 15 minutes and then was dried over anhydrous magnesium sulphate. The drying agent was removed by suction filtration and the filtrate was concentrated under reduced pressure. The crude product obtained was subjected to column chromatography (50% EtOAc-hexane) to afford 21 mg (50%) of the title compound.

^{1}H NMR ($CDCl_3$) δ: 2.11 (s, 3H), 2.22-2.35 (m,1H), 3.16 (d, 1H, J=11.6 Hz), 3.33 (d of d, 1H, J=4.2, 11.6 Hz), 3.70-3.92 (m,2H), 5.46-5.54 (m,1H), 6.69 (d, 1H, J=4.2 Hz).

EXAMPLE 12

CIS AND *TRANS*-2-BENZOYLOXYMETHYL-5-METHOXYCARBONYLOXY -1,3-OXATHIOLANE



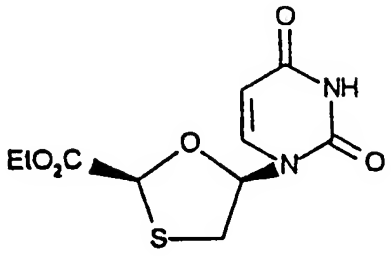
A solution of 17.93 g (0.118 mmol) of mercaptoacetaldehyde dimer and 38.70 g (0.236 mmol) of benzoyloxyacetaldehyde in 57.3 mL (3 eq) of pyridine was heated until all the solid dissolved. After cooling, 300 mL of anhydrous methylene chloride were added and the mixture was cooled at 0°C for ca. 30 minutes. To this solution at 0°C, was slowly added a solution of methylchloroformate (57.3 mL, 0.71 mmol) in 80 mL of methylene chloride. The mixture was stirred for 12 hrs and diluted with ca. 200 mL of methylene chloride and washed several times with brine to remove pyridinium salt and then the organic layer was washed with water. The organic layer was dried over magnesium sulphate at 0°C and then filtered. Residual pyridine was removed *in vacuo* and the organic residue was purified by flash chromatography using hexanes:ethyl acetate (2:1) as eluent to yield a mixture of 2:1 *trans:cis* carbonates (56.3 g, 80%).

^{1}H NMR ($CDCl_3$) δ 3.25 (d, 1H, J=3.1 Hz), 3.30 (dd, 1H, J=3:1 Hz), 3.73 (s, 0.1 H), 3.75 (s, 2 H), 4.47 (m, 2H), 5.66 (m, 2H), 6.50 (brd, 0.33H), 6.56 (d, 0.66H, J=3.81 Hz), 7.38 (d, 2H, J=7.3 Hz), 7.51 (t,1H, J=7.2 Hz), 8.00 (dd, 2H, J=7.3 Hz).

^{13}C NMR ($CDCl_3$) *trans* isomer δ 36.9, 54.6, 65.7, 83.2, 101.9, 126.3, 128.4, 128.5, 133.1, 154.3, 166.0, *cis* isomer δ 37.6, 54.6, 67.3, 84.7, 102.1, 126.3, 128.4, 128.5, 133.1, 154.3, 165.9.

EXAMPLE 13

CIS-2-CARBOETHOXY-5-(URACIL-1'-YL)-1,3- OXATHIOLANE

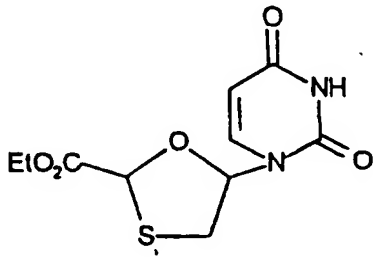


To a stirred solution of the acetate (468 mg, 2.13 mmol) as obtained in example 10 and *bis*-silylated uracil (653 mg, 1.2 equivalents) in dichloromethane under argon was added trimethylsilyl iodide (303 μL, 1 equivalent). The resultant yellow solution was stirred for 6.5 hours at room temperature. As indicated by TLC (silica gel), all starting material was consumed. The reaction was quenched with a 1:1 mixture of saturated solutions of sodium bicarbonate and sodium thiosulphate (5 mL). After 15 minutes of stirring, the mixture was transferred to a separatory funnel with the aid of more dichloromethane (30 mL). The aqueous phase was removed and the organic layer was washed with saturated sodium bicarbonate-sodium thiosulphate solution 1:1, 10 ml, water (10 mL), brine (10 mL), and then was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the crude product which was triturated with a 1:1 mixture of ethyl acetate-hexane (about 10 mL). The precipitate was collected by suction filtration and then was dried under vacuum to afford 346 mg (60%) of the nucleoside as a crystalline white solid. Analysis of the triturate by TLC showed that it contained the desired product but no attempt was made to isolate these compound. The 300 MHz proton NMR spectrum of the product indicated that it consisted of one isomer only.

^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H, J=7.2 Hz), 3.16 (dd, 1H, J=7.7 Hz), 3.42 (dd, 1H, J=4.8, 12.0 Hz), 4.29 (q, 2H, J=7.1 Hz), 5.82 (dd, 1H, J=2.1, 8.2 Hz), 6.46 (dd, 1H, J=4.7, 7.5 Hz), 8.32 (d, 1H, J=8.2 Hz), 8.53 (brs, 1H)
^{13}C NMR ($CDCl_3$) δ 14.2, 35.4, 62.8, 78.1, 89.5, 103.5, 140.8, 151.1, 163.9, 170.9

EXAMPLE 14

***CIS*-2-CARBOETHOXY-5-(URACIL-1'-YL)-1,3- OXATHIOLANE**

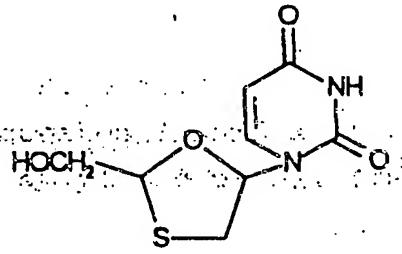


To a stirred solution of a mixture of the *cis* and *trans* carbonates (Example 9)(4:1 by NMR) (60 mg, 0.254 mmol) and silylated uracil (78 mg, 1.2 equivalents) in dry dichloromethane (1.5 mL) under argon was added TMS-I (36 μL, 1.0 equivalent). The resultant light yellow suspension was stirred at room temperature for 80 minutes at which time all starting material was consumed (TLC). The reaction was quenched with a 1:1 mixture (1 mL) of saturated sodium bicarbonate and sodium thiosulphate followed by dilution with dichloromethane (4 mL). The mixture was stirred until a colorless biphasic suspension was obtained. This suspension was transferred to a separatory funnel with the aid of more dichloromethane (25 mL) and was washed with saturated sodium thiosulphate, brine, and then was dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* provided the crude product. Trituration of the crude product with a 1:1 mixture (3 mL) of dichloromethane and ethyl acetate gave a white solid which was collected by suction filtration and was dried

under vacuum (31 mg). The NMR spectrum of this material indicated that it consisted of the *cis* nucleoside only. The triturate was concentrated under reduced pressure and then was subjected to flash column chromatography (1:1 ethyl acetate-dichloromethane) to produce another 8 mg of white solid. The NMR spectrum of this substance showed that it was a 2.5:1 mixture of the *cis* and *trans* nucleosides favouring the *cis* isomer. The total yield of this reaction was 58% and the stereoselectivity was about 13:1 in favour of the *cis* isomer which displayed the same physical data as reported in Example 13.

EXAMPLE 15

***CIS*-2-HYDROXYMETHYL-5-(URACIL-1'-YL)-1,3- OXATHIOLANE**



To a stirred solution of the condensation product obtained in examples 13 or 14, (33 mg, 0.107 mmol) in a solvent mixture (2:1) of dichloromethane-methanol (1.5 mL) at room temperature under argon was introduced sodium borohydride (8 mg, 2 equivalents). The resulting mixture was stirred for 1 hour. Analysis of the reaction mixture by TLC indicated that substantial amount of starting material was present. More hydride (approx. 10 mg) was added and stirring was continued for another 1.5 hours. The excess hydride was quenched by addition of one drop of saturated ammonium chloride solution. After dilution with tetrahydrofuran (3 mL), the gelatinous mixture was stirred for 30 minutes. The inorganic salt was removed by suction filtration through a pad of celite. Concentration of the filtrate under reduced pressure provided the crude product which was

subjected to column chromatography (100% ethyl acetate, silica gel) to afford the desired alcohol (25 mg, 90%) as a white solid.

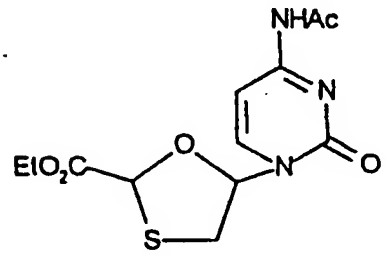
The 300 MHz proton NMR spectrum of the compound thus obtained was found to be identical to that prepared according to different procedures. Thus, the stereochemistry of the nucloside generated by this new route was established.

^{1}H NMR (DMSO) δ 3.23 (d of d, 1H, J=4.4, 12.0 Hz), 3.45 (d of d, 1H, J=5.6, 11.9 Hz), 3.75 (d, 2H, J=4.4 Hz), 5.20 (t, 1H, J=4.4 Hz), 5.36 (brs, 1H), 5.65 (d of d, 1H, J=2.1, 8.2 Hz), 6.21 (t, 1H, J=5.1 Hz), 7.92 (d, 1H, J=8.2 Hz).

^{13}C NMR (DMSO)= δ 36.02, 62.54, 85.91, 86.48, 101.82, 141.05, 150.63, 163.71.

EXAMPLE 16

***CIS*-2-CARBOETHOXY-5-(N-ACETYLCYTOSIN-1'-YL)-1,3-OXATHIOLANE**

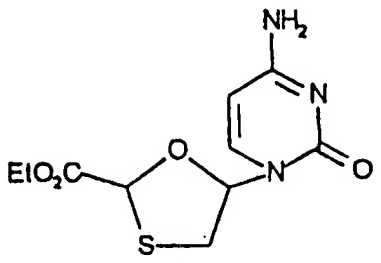


To a stirred suspension of N-acetylcytosine (237 mg, 1.40 mmol) in dichloromethane (2.5 mL) containing 2,6-lutidine (326 μL, 1.40 mmol) was added slowly trimethylsilyl trifluoromethanesulphonate (540 μL, 3.07 mmol). The resultant mixture was stirred for 15 minutes to give a homogeneous solution. A mixture of *cis* and *trans*-2-carboethoxy-5-methoxycarbonyloxy-1,3-oxathiolane (example 9) (300 mg, 1.27 mmol), dissolved in dichloromethane (2 mL), was introduced to the above solution followed by the addition of iodotrimethylsilane (181 μL, 1.27 mmol). The reaction mixture was kept at

room temperature for 1 hour and 40 minutes. Water (2 mL), saturated sodium thiosulphate (4 mL) and dichloromethane (6 mL) were added to quench the reaction. The resulting mixture was stirred vigorously for 10 minutes and then was transferred to a separatory funnel with the aid of more dichloromethane (30 mL). The aqueous phase was removed and the organic phase was washed successively with saturated sodium thiosulphate (10 mL), water (10 mL), 1 M hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), brine (10 mL), and then was dried (sodium sulphate). The solvent was evaporated under reduced pressure to give the crude product as a light yellow solid (395 mg). The ^{1}H NMR spectrum of this material indicated that a 7.5:1 (in favour of the *cis* isomer) mixture of the expected coupling products was obtained. This material was triturated with a mixture of dichloromethane (1.5 mL) and a solution of ethyl acetate-hexane (1:1) (6 mL). The white solid formed was collected by suction filtration and was dried under vacuum to afford 262 mg (63% yield) of the desired product as a white powder. The ^{1}H NMR spectrum of the substance indicated an isomeric purity of greater than 95%. The triturate was concentrated and then was subjected to flash column chromatography (5% MeOH-EtOAc) to provide another 58 mg (14% yield) of the nucleosides as a 1:1 mixture of the *cis* and *trans* isomers (^{1}H NMR). The title compound displayed the following spectral characteristics: ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J=7.1 Hz), 2.28 (s, 3H), 3.23 (d of d, 1H, J=12.3, 6 Hz), 3.68 (d of d, 1H, J=12.4, 4.8 Hz), 4.31 (q, 2H, J=7.1 Hz), 5.56 (s, 1H), 6.43 (t, 1H, J=5.2 Hz), 7.17 (d, 1H, J=7.5 Hz), 8.76 (br. d, 1H, J=7.4 Hz), 8.30-9.00 (unresolved m, 1H).

EXAMPLE 17

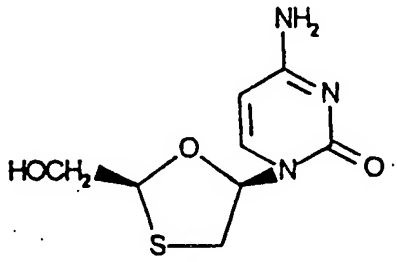
CIS-2-CARBOETHOXY-5-(CYTOSIN-1'-YL)-1,3- OXATHIOLANE



A mixture of *cis*-2-carboethoxy-5-(N4'-acetylcytosin-1'-yl)-1,3-oxathiolane (example 16) (20 mg, 0.061 mmol) in ethanol (1 mL) containing trifluoroacetic acid (9.4 μL, 0.25 mmol) was refluxed under argon for 3 hours and 10 minutes. On cooling to room temperature, a crystalline white solid was formed. This solid was collected by suction filtration and was dried under vacuum to afford 15 mg (86%) of the desired product. The title compound displayed the following spectral characteristics: ^{1}H NMR (DMSO) δ 1.23 (t, 3H, J=7.1 Hz), 3.32 (d of d, 1H, J=12.4, 5.2 Hz), 3.63 (d of d, 1H, J=12.3, 5.2 Hz), 4.21 (q, 2H, J=7.1 Hz), 5.80 (s, 1H), 6.08 (d, 1H, J=7.7 Hz), 6.32 (t, 1H, J=5.1 Hz), 8.19 (d, 1H, J=7.7 Hz), 8.35 (brs, 1H), 9.12 (brs, 1H).

EXAMPLE 18

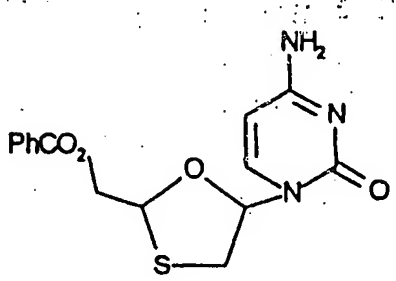
CIS-2-HYDROXYMETHYL-5-(CYTOSIN-1'-YL)-1,3- OXATHIOLANE (BCH-189)



To a stirred suspension of *cis*-2-carboethoxy-5-(cytosin-1'-yl)-1,3-oxathiolane (Example 17) (36 mg, 0.125 mmol) is ethanol at 0°C under argon was added sodium borohydride (9.5 mg, 0.250 mmol). The resultant mixture was stirred for 2 hours 30 minutes at (0°C to RT). The reaction was quenched by the addition of one drop of concentrated ammonium hydroxide, followed by dilution with methanol (1 mL). After the mixture had been stirred for 15 minutes, the solvent was removed under reduced pressure. The crude product thus obtained was subjected to column chromatography (25% MeOH-EtOAc) to afford 26 mg (85%) of the desired product. The title compound displayed spectral characteristics identical to that reported for BCH-189.

EXAMPLE 19

***CIS* AND *TRANS* 2-BENZOYLOXYMETHYL-5-(CYTOSIN-1'-YL) -1,3-OXATHIOLANE**



To a solution maintained at 0°C of 2.14 g (7.2 mmol) of carbonate (as in example 7) in 10 mL of freshly distilled 1,2-dichloroethane was added 0.37 g (0.36 mmol) of fused $ZnCl_2$ and 2.7 mL (2.7 mmol) of $TiCl_4$. After stirring for 5 minutes a solution of silylated cytosine (from 1 g of cytosine silylated with 1,1,1,3,3,3,-hexamethyldisilazane) in 25 mL of freshly distilled 1,2-dichloroethane was added via a canula (10 -15 min.) The reaction was allowed to warm to RT (3 hours) and stirring continued for 11 hours followed by a short reflux (20 min). The solution was then cooled and quenched with saturated sodium bicarbonate (30 mL).

After stirring for 15 min. the two phase solution was separated and the organic layer together with the emulsion was filtered through a celite. The aqueous layer was extracted (3 X 20 mL) with CH_2Cl_2 and the combined organic layers were washed with brine, separated and dried over $MgSO_4$. The oil obtained from the organic layer, by evaporation of the solvents *in vacuo*, was purified by chromatography on silica gel using gradient elution (1:1 hexanes:EtOAc - 9:1 EtOAc: MeOH) to yield 1.32 g of *trans* and *cis* isomers (*trans/cis* = 3.5/5 as determined by ^1H NMR).

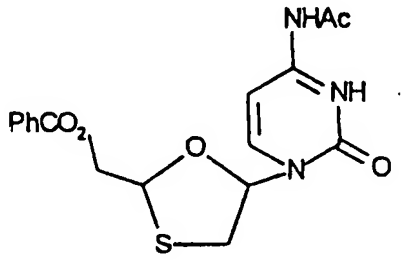
Spectral properties were identical to those reported earlier.

By varying the amount and the nature of the Lewis acid the yield and the ratio of the *trans* to *cis* isomers were as follows:

Lewis Acid	Yield	trans/cis ratio
0.25 eq. TiCl4	31 %	1 / 1.2
0.40 eq. TiCl4	50 %	1 / 1.3
0.3 eq. TiCl4 0.2 eq. ZnCl2	60 %	1 / 1.6

EXAMPLE 20

CIS AND *TRANS* 2-BENZOYLOXYMETHYL-5-(N4'-ACETYL CYTOSIN-1'-YL)-1,3-OXATHIOLANE



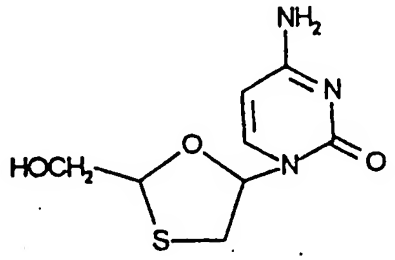
To a solution maintained at 0°C of 2.14 g (7.2 mmol) of *trans* 2-benzoyloxymethyl-5-acetoxy-1,3-oxathiolane (as in Example 3) in 10 mL of freshly distilled acetonitrite

was added a solution of silylated cytosine N-acetylcytosine (from 1.37 g of N-acetylcytosine silylated with 1,1,1,3,3,3,-hexamethyldisilazane) in 25 mL of freshly distilled 1,2-dichloroethane via a canula (10 -15 min.) and 0.2 mL of iodotrimethylsilane. The reaction was allowed to stir at 0°C (3 hours) and stirring continued for 11 hours at RT. The solution was then cooled and quenched with saturated sodium bicarbonate (30 mL). After stirring for 15 min. the two phase solution was separated and the organic layer together with the emulsion was filtered through a celite. The aqueous layer was extracted (3 X 20 mL) with CH_2Cl_2 and the combined organic layers were washed with brine, separated and dried over $MgSO_4$. The oil obtained from the organic layer, by evaporation of the solvents *in vacuo*, was purified by chromatography on silica gel using gradient elution (1:1 hexanes:EtOAc - 9:1 EtOAc: MeOH) to yield 2.43 g of *trans* and *cis* isomers (*trans/cis* = 3/7 as determined by ^1H NMR). The physical properties are identical to those reported earlier.

Replacement of iodotrimethylsilane by trimethylsilyltriflate in dichloromethane at RT yielded 2.43 g of *trans* and *cis* isomers in 1:1 ratio as determined by ^1H NMR.

EXAMPLE 21

CIS-2-HYDROXYMETHYL-5-(CYTOSIN-1-YL)-1,3-OXATHIOLANE

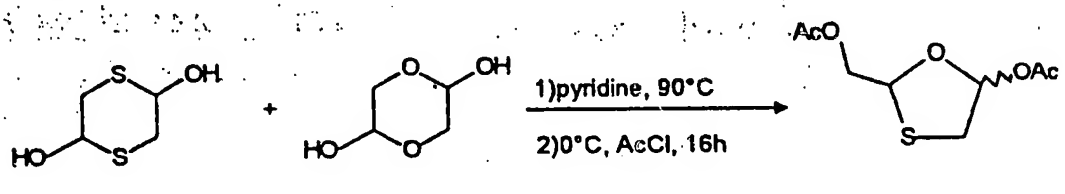


A suspension of *cis*-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane (200g, 0.54 mol) and Amberlite IRA

400 (OH) ion-exchange resin (600g) in IMS was stirred and heated to 60-65°C. The suspension was maintained at this temperature range for 1 hour, and filtered hot. The resin was washed with IMS at 60°C (200 mL).
The combined filtrates were filtered twice through celite J2 and the celite washed sequentially with IMS at 60°C (200 mL) and water at 50-60°C (100 mL).
The combined filtrates were distilled under atmospheric pressure to a volume of 500 mL. Absolute ethanol was added, and the distillation continued until a further 700 mL had been removed. The resultant suspension was allowed to cool, and then stirred overnight at 0-5°C. The suspension was filtered, the product washed with IMS at 0°C (2 x 25 mL), and dried overnight *in vacuo* at 45-50°C to give the title compound, 81.9 g.

EXAMPLE 22.

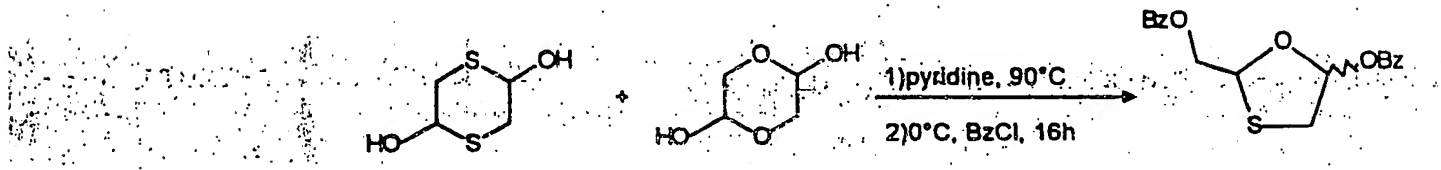
CIS- AND *TRANS*-2-ACETOXYMETHYL-5-ACETOXY-1,3-OXATHIOLANE



A mixture of glycoaldehyde (1.2g, 0.01 mol) and mercaptoacetaldehyde dimer (1.52g, 0.01 mol) in dry pyridine (20 ml) was heated at 90°C for 2 h. The clear solution was then cooled in an ice-bath to 0°C, followed by adding acetyl chloride (2.8 ml). The mixture was stirred at room temperature overnight (16 h), and poured into saturated aqueous $NaHCO_3$ solution (100 ml). The product was extracted into methylene chloride (3 x 100 ml), washed with water (2 x 100 ml), dried over $MgSO_4$ and filtered. The solvent was removed on an evaporator and the oily residue was purified on silica gel hexane:EtOAc 9:1 as eluant to give the product (2.8g) in 59% yield as a mixture of 1:1 *cis*:*trans* isomers.

^{1}H-NMR (300MHz, $CDCl_3$): δ in ppm
6.68 (d, 1H, H-5, trans-isomer, J=4.1 Hz)
6.61 (d, 1H, H-5, cis-isomer, J=4.4 Hz)
5.52 (m, 2H, H-2, cis and trans-isomers)
4.37 (dd, 1H, $-CH_2OAc$, cis-isomer, J=8.0 and 11.7 Hz)
4.26 (m, 2H, $-CH_2OAc$, trans-isomer)
4.13 (dd, 1H, $-CH_2OAc$, cis-isomer, J=4.1 and 11.8 Hz)
3.33 (dd, 2H, H-4, cis and trans isomers)
3.11 (dd, 2H, H-4, cis and trans-isomers)
2.11 (s, 3H, CH_3-)
2.08 (s, 3H, CH_3-)

EXAMPLE 23.
CIS- AND *TRANS*-2-BENZOYLOXYMETHYL-5-BENZOYL-1,3-OXATHIOLANE



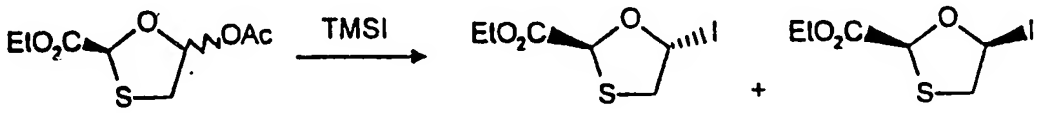
A mixture of glycoaldehyde (1,2g, 0.01 mol) and mercaptoacetaldehyde dimer (1.52g, 0.01 mol) in dry pyridine (20 ml) was heated at 90°C for 2h. The clear solution was then cooled in an ice-bath to 0°C, followed by adding benzoyl chloride (4.6 ml). The mixture was stirred at room temperature overnight (16h), and poured into saturated aqueous $NaHCO_3$ solution (100 ml). The product was extracted into methylene chloride (3 x 100 ml), washed with water (2 x 100 ml), dried over $MgSO_4$ and filtered. The solvent was removed on an evaporator and the oily residue was purified on silica gel using hexane:EtOAc 9:1 as eluant to give the product (3.65g) in 53% yield as a mixture of 1:1 cis and trans isomers.

^{1}H-NMR (300 MHz, $CDCl_3$): δ in ppm
8.05 (m, aromatic)
7.57 (m, aromatic)

7.45 (m, 4H, aromatic)
6.98 (d, 1H, H-5, trans-isomer, J=3.9 Hz)
6.90 (d, 1H, H-2, cis-isomer, J=3.0 Hz)
5.79 (t, 1H, H-2, trans-isomer, J=5.2 Hz)
5.74 (dd, 1H, H-2, cis-isomer, J=4.9 and 7.3 Hz)
4.58 (m, 4H, $-CH_2OBz$, cis and trans-isomers)
3.45 (m, 2H, H-4, cis and trans isomers)
3.35 (m, 2H, H-4, cis and trans-isomers).

EXAMPLE 24.

CIS- AND *TRANS*-ETHYL 5-IODO-1,3-OXATHIOLAN-2-CARBOXYLATE



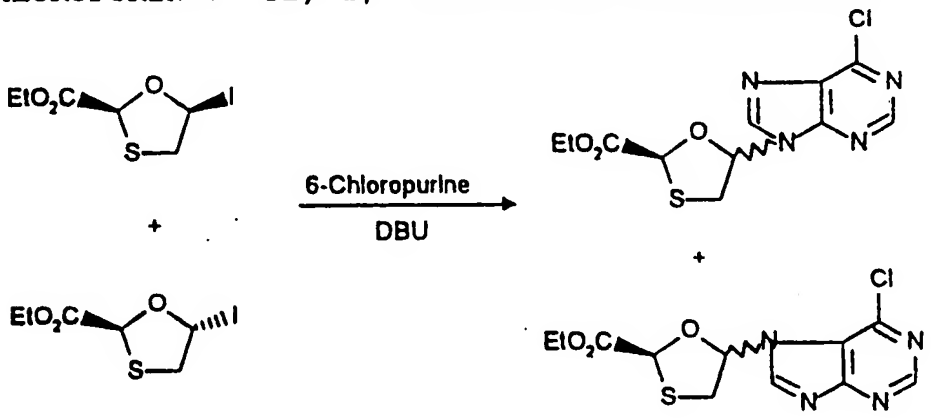
The starting material (21.5 mg, 0.0976 mmol, *cis*:*trans*=1:1) in dichloromethane-d_2 (0.6 mL) at -78°C under argon atmosphere wa treated with iodotrimethylsilane (0.014 mL, 0.0976 mmol). The slightly yellow solution was left at room temperature for two hours. The starting acetoxyoxathiolane compounds were completely converted to the iodo intermediates and trimethylsilyl acetate. The iodo compounds (in a 6.7:1 ratio of *cis* to *trans* isomer) are unstable to the moisture and had to be used without any purification.

^1H NMR (CD_2Cl_2): δ 0.00 (s, 9H), 1.05 (t, 3H, J=7.1Hz), 1.80 (s, 3H), 3.25-3.50 (m, 2H), 4.00 (q, 2H, J=7.1Hz), 5.43 (s, 0.13H), 5.48 (s, 0.87H) 6.64 (ddd, 0.13H, J=4.3, 2.9, 0.7 Hz), 7.00 (dt, 0.87H, J=4.0, 0.7 Hz);

^{13}C NMR (CD_2Cl_2): δ 0.3, 2.5, 14.8, 23.5, 47.7, 48.2, 63.1, 65.5, 69.7, 81.6, 83.7, 168.6.

EXAMPLE 25.

CIS- AND *TRANS*-ETHYL 5-(6'CHLOROPURIN-9'-YL)-1,3-OXATHIOLAN-2-CARBOXYLATE; and *CIS*- AND *TRANS*-ETHYL 5-(6'CHLOROPURIN-7'-YL)-1,3-OXATHIOLAN-2-CARBOXYLATE



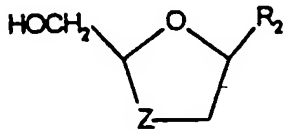
To the 6-chloropurine (15 mg, 0.0976 mmol) in dichloromethane-d_2 (0.15 mL) at room temperature under argon atmosphere was added 1,8-diazabicyclo[5,4,0] undec-7-ene (0.015 mL, 0.0976 mmol). The solution thus formed was added to the iodo intermediates prepared above in dichloromethane-d_2 at -78°C. The mixture was allowed to stay at room temperature for 4 hours and then diluted with dichloromethane (20 mL), washed with saturated aqueus sodium bicarbonate, 1N aqueous hydrogen chloride, water and brine, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate-dichloromethane to afford the N-9 linked isomers (11.6 mg, 38%, *cis*:*trans*=11:1) and N-7 linked isomers (4.4 mg, 14.3%, *cis*:*trans*=8.4:1).

^{1}H NMR for N-9 isomers ($CDCl_3$): δ 1.26 (t, 3H, J=7.1 Hz), 3.65 (m, 2H), 4.26 (q, 2H, J=7.1 Hz), 5.62 (s, 0.92H), 5.80 (s, 0.08H), 6.75 (t, 0.92H, J=5.4 Hz), 7.02 (dd, J=6.2, 2.0 Hz), 8.39 (s, 0.08H), 8.73 (s, 0.92 Hz), 8.89 (s, 0.92 Hz);
^{1}H NMR for the N-7 isomers ($CDCl_3$): δ 1.30 (t, 3H, J=7.1 Hz), 3.38 (d, 0.12H, J=12.5 Hz), 3.54 (dd, 0.88H, J=12.5, 4.5 Hz), 3.75 (dd, 0.88H, J=14.5, 4.5 Hz), 3.96 (dd, 0.12H, J=12.5, 4.5 Hz), 4.29 (q, 2H, J=7.1 Hz),

5.69 (s, 0.88H), 5.90 (s, 0.12H), 7.07 (t, 0.88H, J=4.5 Hz), 7.35 (d, 0.12H, J=4.5 Hz), 8.45 (s, 0.12H), 8.92 (s, 1H), 9.20 (s, 0.88H)

CLAIMS:

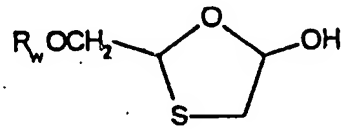
1. A process for preparing an oxathiolane of formula (I), pharmaceutically acceptable salts or esters, and geometric and optical isomers thereof:



(I)

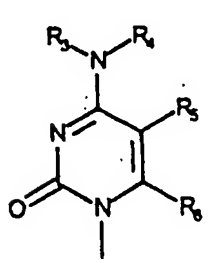
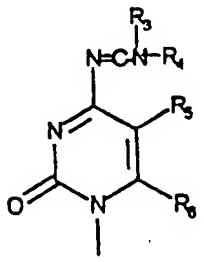
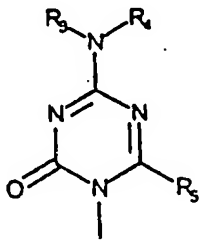
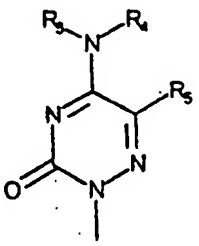
wherein:
R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and Z is S, S=O or SO_2;

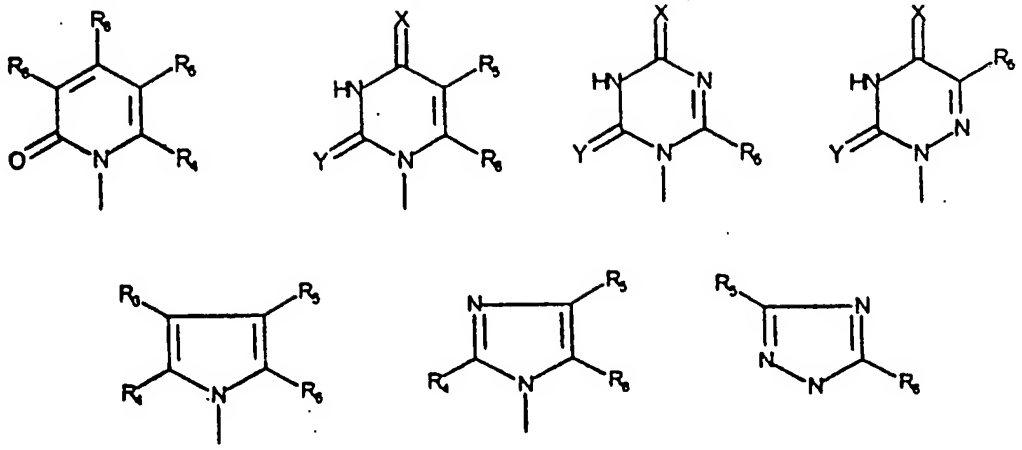
-the process comprising the step of reacting a mercaptoacetaldehyde with a compound having formula R_WOCH_2CHO, wherein R_W is hydrogen or R_1, wherein R_1 is a hydroxyl protecting group,
under neutral or basic conditions to obtain an intermediate of formula (XIII):



(XIII)

2. The process according to claim 1, wherein in formula (I), R_2 is a purine or pyrimidine base selected from the group consisting of:



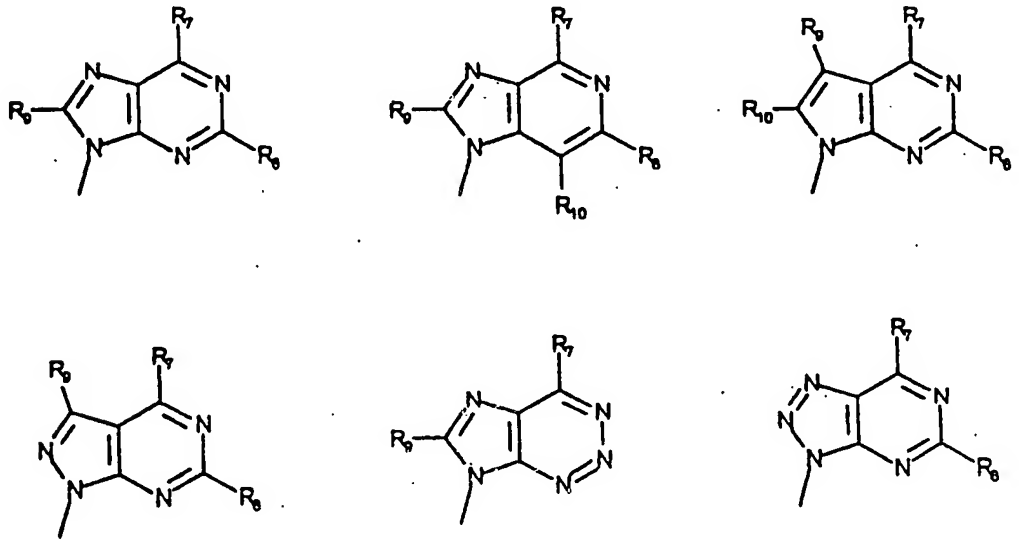
wherein:

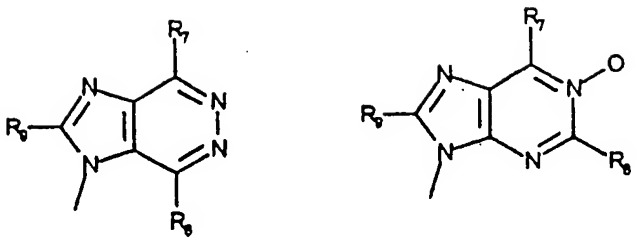
X is oxygen or sulfur; Y is oxygen or sulfur;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, substituted or unsubstituted C_{1-6} alkyl, or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyl or aracyl;

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, cyano, carboxy, carbamoyl, alkoxycarbonyl, hydroxymethyl, trifluoromethyl, thioaryl, substituted or unsubstituted C_{1-6} alkyl or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyloxy;

and



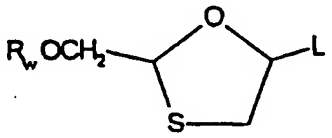


wherein:

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, alkoxy, thiol, thioalkyl, amino, substituted amino, halogen, cyano, carboxy, alkoxycarbonyl, carbamoyl, substituted or unsubstituted C_{1-6} alkyl, or alkenyl, or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy; and

R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, alkoxy, amino, substituted amino, halogen, azido, substituted or unsubstituted C_{1-6} alkyl or alkenyl or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy.

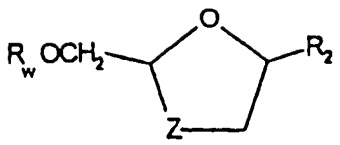
3. The process according to claim 1 or 2, wherein the hydroxyl of the intermediate of formula (XIII) is converted to a suitable leaving function L to obtain an intermediate of formula (XIV):



(XIV)

wherein, R_W is hydrogen or R_1, wherein R_1 is a hydroxy protecting group, and L is OR where R is an acyl having 1 to 16 carbon atoms unsubstituted or substituted with a heteroatom.

4. The process according to claim 3, further comprising the step of reacting the intermediate of formula (XIV) with a silylated pyrimidine or purine base or an analogue thereof, in the presence of a Lewis acid to produce a compound of the formula (IX):



(IX)

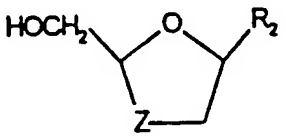
wherein R_2 and R_w have the same meaning as in claim 3, and Z is S.

5. The process according to claim 4, wherein the sulfur of the intermediate of formula (IX) may optionally be oxidized to give an intermediate of formula (IX) wherein Z is S=O or SO_2.

6. The process according to claim 1 or 2, wherein the mercaptoacetaldehyde is obtained from a mercaptoacetaldehyde dimer dissolved in an inert solvent.

7. The process according to claim 6, wherein the inert solvent is selected from the group consisting of: pyridine, toluene and DMSO.

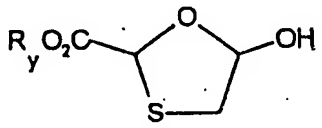
8. A process for preparing an oxathiolane of formula (I), pharmaceutically acceptable salts or esters, and geometric isomers thereof, and mixtures of those isomers:



(I)

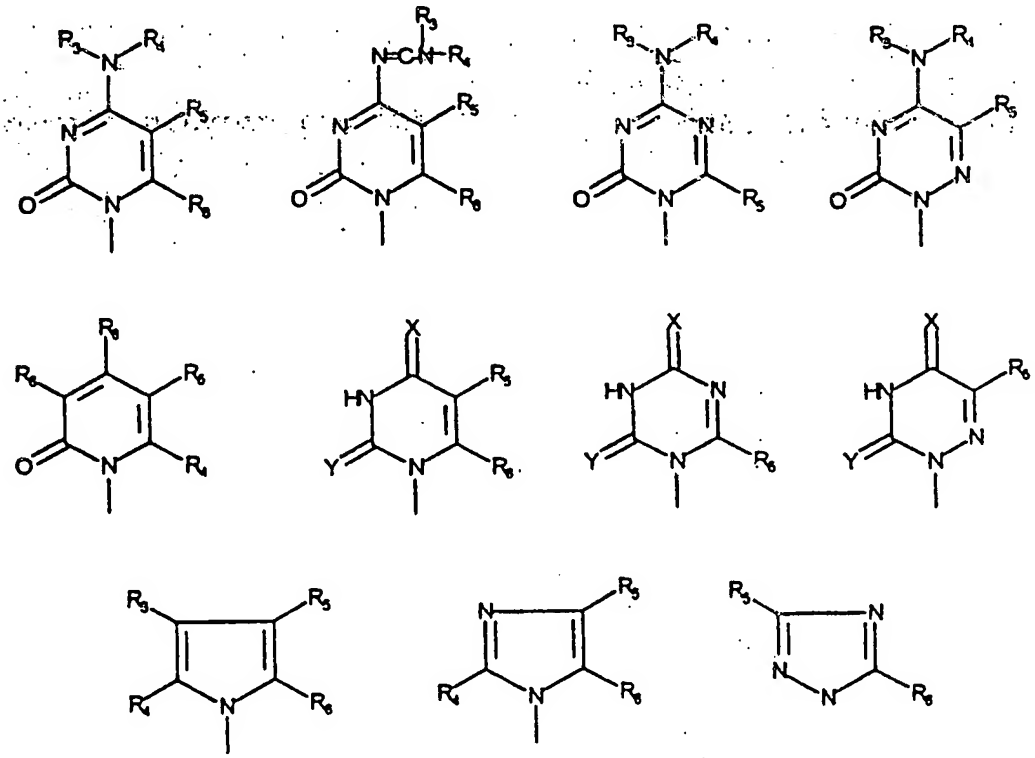
wherein:
R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and
Z is selected from a group consisting of S, S=O and SO_2;

-the process comprising the step of reacting a mercaptoacetaldehyde with a compound having formula $R_yOOCCHO$, wherein R_y is substituted or unsubstituted C_{1-12} alkyl or substituted or unsubstituted C_{6-20} aryl to obtain an intermediate of formula (XV):



(XV)

9. The process according to claim 8, wherein, in the formula (I), R_2 is selected from the group consisting of:



wherein:

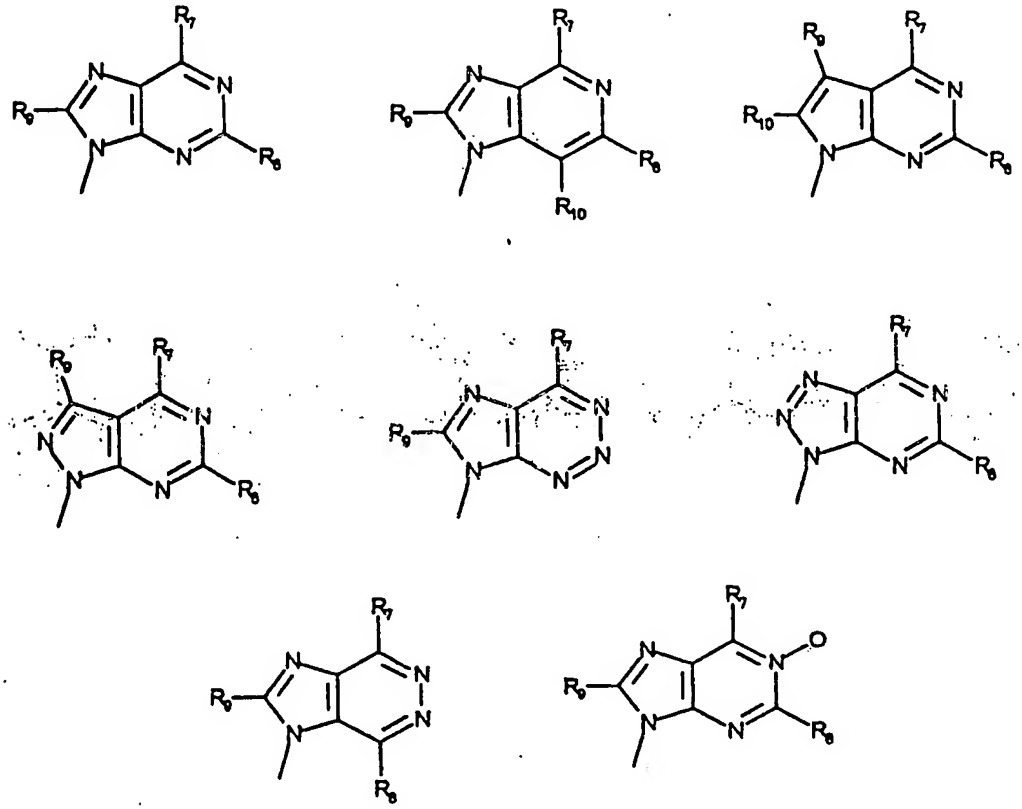
X is oxygen or sulfur; Y is oxygen or sulfur;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, amino, substituted or

unsubstituted C_{1-6} alkyl, or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyl or aracyl;

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, cyano, carboxy, carbamoyl, alkoxycarbonyl, hydroxymethyl, trifluoromethyl, thioaryl, substituted or unsubstituted C_{1-6} alkyl or C_{1-6} alkenyl or C_{1-6} alkynyl, and substituted or unsubstituted C_{1-10} acyloxy;

and



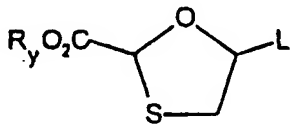
wherein:

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, alkoxy, thiol, thioalkyl, amino, substituted amino, halogen, cyano, carboxy, alkoxycarbonyl, carbamoyl, substituted or unsubstituted C_{1-6} alkyl, or alkenyl, or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy; and

R_9 and R_{10} are independently selected from the group consisting of hydrogen, hydroxy, alkoxy, amino, substituted amino, halogen, azido, substituted or

unsubstituted C_{1-6} alkyl or alkenyl or alkynyl, and substituted or unsubstituted C_{1-10} acyloxy.

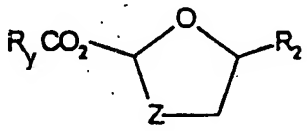
10. The process according to claim 8 or 9, further comprising the step of converting the hydroxyl of the intermediate of formula (XV) to a suitable leaving function L to obtain an intermediate of formula (XVI):



(XVI)

wherein R_y is as defined in claim 8, and L is a leaving group OR where R is an acyl having 1 to 16 carbon atoms unsubstituted or substituted with a heteroatom.

11. The process according to claim 10, further comprising the step of reacting the intermediate of formula (XVI) with a silylated base or an analogue thereof, in the presence of a Lewis acid to produce a compound of formula (XVII):

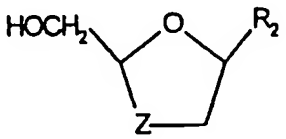


(XVII)

wherein Z is S, and R_y has the same meaning as in claim 10, and R_2 is a purine or pyrimidine base, an analogue or derivative thereof.

12. The process according to claim 11, wherein the sulfur of the intermediate of formula (XVII) may optionally be oxidized to give an intermediate of formula (XVII) wherein Z is S=O or SO_2.

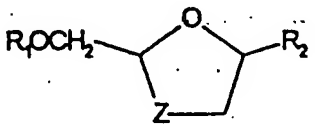
13. The process according to claim 12, further comprising the step of reducing the intermediate of formula (XVII) to a compound of formula (I):



(I)

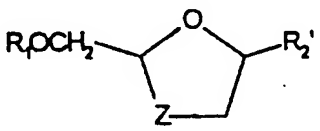
wherein:
R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and
Z is selected from a group consisting of S, S=O and SO_2.

14. The process according to claim 13, further comprising the steps of:
(a) protecting the hydroxyl group of the compound of formula (I) with a suitable protecting function R_1 to obtain an intermediate of formula (XIX):



(XIX)

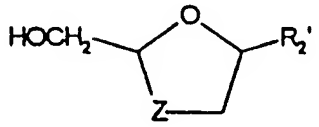
wherein R_1 is selected from the group consisting of: C_{1-16} acyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl;
(b) interconverting the purine or pyrimidine base substituent or analogue thereof R_2 of formula (XIX) to another pyrimidine or purine base or analogue thereof R_2' to obtain an intermediate of formula (XX):



(XX)

and

(c) removing the protecting function R_1 of the intermediate of formula (XX) to obtain a compound of formula (I):



(I)

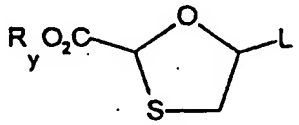
wherein Z and R_2 are as defined in claim 13.

15. The process according to claim 8 or 9, wherein the mercaptoacetaldehyde is obtained from a mercaptoacetaldehyde dimer dissolved in an inert solvent.

16. The process according to claim 15, wherein the inert solvent is selected from the group consisting of: pyridine, toluene, and DMSO.

17. The process according to claim 8 or 9, further comprising the steps of:

(a) converting the hydroxyl of the intermediate of formula (XV) to a suitable leaving function L to obtain an intermediate of formula (XXI):

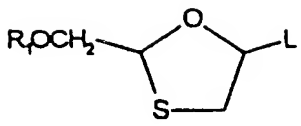


(XXI)

wherein R_y is substituted or unsubstituted C_{1-12} alkyl or substituted or unsubstituted C_{6-20} aryl, L is OR where R is an acyl having from 1 to 16 carbon atoms unsubstituted or substituted with a heteroatom;

(b) converting the carboxyl to a hydroxymethyl function; and

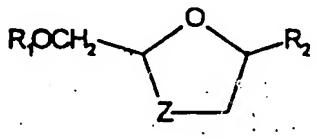
(c) protecting the resulting hydroxymethyl with a suitable protecting function R_1 to obtain an intermediate of formula (XXII):



(XXII)

wherein R_1 is selected from the group consisting of: C_{1-16} acyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl.

18. The process according to claim 17, further comprising the step of reacting the intermediate of formula (XXII) with a silylated pyrimidine or purine base or an analogue thereof, in the presence of a Lewis acid to obtain an intermediate of formula (XXIII):

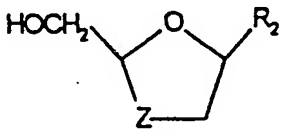


(XXIII)

wherein R_1 is as defined in claim 21, R_2 is a purine or pyrimdine base, analogue or derivative thereof, and Z is S.

19. The process according to claim 18, wherein the intermediate of formula (XXIII) is optionally oxidized to obtain an intermediate of formula (XXIII) wherein Z is S=O or SO_2.

20. The process according to claim 19, further comprising the step of removing the hydroxyl protecting function R_1 from compound (XXIII) to obtain a compound of formula (I):



(I)

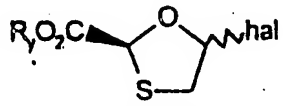
wherein Z is S, S=O, or SO_2, and R_2 is a purine or pyrimidine base or an analogue or derivative thereof.

21. The process according to claim 4, wherein the Lewis acid is selected from the group consisting of: TMSOTf, TMSI, $TiCl_4$, and $SnCl_4$.

22. The process according to claim 11, wherein the Lewis acid is selected from the group consisting of: TMSOTf, TMSI, $TiCl_4$, and $SnCl_4$.

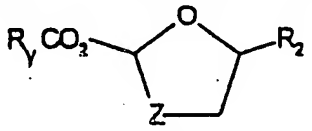
23. The process according to claim 18, wherein the Lewis acid is selected from the group consisting of: TMSOTf, TMSI, $TiCl_4$, and $SnCl_4$.

24. The process according to claim 10, further comprising the steps of:
a) reacting the intermediate of formula (XVI) with a halogen-containing silyl Lewis acid to obtain an intermediate of formula (XXVI):



(XXVI)

wherein hal is halogen, and
b) coupling the intermediate of formula (XXVI) with a base or analogue thereof R_2 under basic conditions, to obtain an intermediate of formula (XVII):



(XVII)

25. The process according to claim 24, wherein said Lewis acid is TMSI.

26. The process according to claim 24 or 25, wherein the R_2 base or analogue thereof is a purine.

27. The process according to claim 26, wherein the purine is 6-chloropurine.

28. Intermediates useful for the production of oxathiolane compounds, said intermediates selected from the group consisting of:
trans-2-hydroxymethyl-5-acetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-hydroxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(4',5'-dichlorobenzoyloxy)-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-trimethylacetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(2',2',2'-trichloroethoxycarbonyloxy)1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-ethoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-methoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-acetoxy-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(N4'-acetyl cytosin-1'-yl)-1,3-oxathiolane;
cis and *trans*-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-hydroxy-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-methoxycarbonyloxy-1,3-oxathiolane;
cis and *trans*-2-carboethoxy-5-acetoxy-1,3-oxathiolane;
cis-2-carboethoxy-5-(N-acetylcytosin-1'-yl)-1,3-oxathiolane;
cis-2-carboethoxy-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis-2-carboethoxy-5-(uracil-1'-yl)-1,3-oxathiolane;
cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
cis- and *trans*-2-benzoyloxymethyl-5-benzoyloxy-1,3-oxathiolane;

cis- and *trans*-2-acetoxymethyl-5-acetoxy-1,3-oxathiolane;
cis- and *trans*-ethyl-5-iodo-1,3-oxathiolan-2-carboxylate;
cis- and *trans*-ethyl-5-(6'-chloropurin-9'-yl)-1,3-oxathiolan-2-carboxylate; and
cis- and *trans*-ethyl-5-(6'-chloropuin-7'-yl)-1,3-oxathiolan-2-carboxylate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 92/00557

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D411/04; C07D473/00; C07D473/40; C07D327/04

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	WO,A,9 111 186 (EMORY UNIVERSITY) 8 August 1991 *Document*	1-27
A	WO,A,9 210 496 (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION INC) 25 June 1992 *Document*	1-28
A	WO,A,9 218 517 (YALE UNIVERSITY) 29 October 1992 *Document*	1-27
A	EP,A,0 515 157 (BIOCHEM PHARMA INC.) 25 November 1992 *Document*	1-28

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° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 AUGUST 1993	27.08.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,9 214 743 (EMORY UNIVERSITY) 3 September 1992 *Document*	1-28
A	WO,A,9 215 308 (THE WELLCOME FOUNDATION LTD) 17 September 1992 *Document*	1-27
A	WO,A,9 208 717 (IAF BIOCHEM INTERNATIONAL INC.) 29 May 1992 *Document*	1-28
A	WO,A,9 117 159 (IAF BIOCHEM INTERNATIONAL INC.) 14 November 1991 cited in the application *Document*	1-28
A	EP,A,0 382 526 (IAF BIOCHEM INTERNATIONAL INC.) 16 August 1990 cited in the application *Document*	1-28

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9200557
SA 68145

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111186	08-08-91	US-A-	5204466	20-04-93
		AU-A-	7300491	21-08-91
		EP-A-	0513200	19-11-92
		US-A-	5210085	11-05-93
WO-A-9210496	25-06-92	US-A-	5179104	12-01-93
		AU-A-	9125991	08-07-92
		AU-A-	9147591	08-07-92
		WO-A-	9210497	25-06-92
WO-A-9218517	29-10-92	None		
EP-A-0515157	25-11-92	AU-A-	1639492	26-11-92
		AU-A-	1639592	26-11-92
		AU-A-	1690892	30-12-92
		AU-A-	1691392	30-12-92
		WO-A-	9220696	26-11-92
		WO-A-	9220669	26-11-92
		CN-A-	1067654	06-01-93
		CN-A-	1067245	23-12-92
		EP-A-	0515156	25-11-92
WO-A-9214743	03-09-92	US-A-	5210085	11-05-93
		AU-A-	1437292	15-09-92
		AU-A-	1561792	15-09-92
		CN-A-	1065065	07-10-92
		WO-A-	9214729	03-09-92
WO-A-9215308	17-09-92	AU-A-	1367692	06-10-92
WO-A-9208717	29-05-92	AU-A-	8864191	11-06-92
WO-A-9117159	14-11-91	AU-A-	7771991	27-11-91
		CN-A-	1058214	29-01-92
		JP-T-	5501117	04-03-93
EP-A-0382526	16-08-90	US-A-	5047407	10-09-91
		AU-B-	630913	12-11-92
		AU-A-	4920190	16-08-90
		CA-A-	2009637	08-08-90

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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16/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0382526		JP-A- 3007282	14-01-91
		OA-A- 9193	30-06-92
		US-A- 5151426	29-09-92